PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 207/327, 207/335, 209/14, 211/90, 213/50, 213/82, 217/16, 217/26, 233/64, 237/28, 237/04, 265/02, 295/185, 401/06, 409/12, A61K 31 /40, 31 /44, 31 /47, 31 /415, 31 /495, 31 /50, 31 /54, 31 /535

A1

(11) International Publication Number: WO 95/29892

(43) International Publication Date: 9 November 1995 (09.11.95)

(21) International Application Number: PCT/US95/05012

(22) International Filing Date: 27 April 1995 (27.04.95)

(30) Priority Data:
08/234,195 28 April 1994 (28.04.94) US
08/423,193 18 April 1995 (18.04.95) US

(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

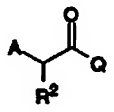
(72) Inventors: DeCICCO, Carl, Peter; 17 Ridgewood Turn, Newark, DE 19711-8300 (US). JACOBSON, Irina, Cipora; Apartment M4, 3360 Chichester Avenue, Boothwyn, PA 19061-3252 (US). MAGOLDA, Ronald, L.; 3 Church Road, Wallingford, PA 19086-6209 (US). NELSON, David, John; 40 Tiverton Circle, Newark, DE 19702-1444 (US). CHERNEY, Robert, Joseph; 104 Bridleshire Court, Newark, DE 19711-2449 (US).

(74) Agents: REINERT, Norbert, F. et al.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

(81) Designated States: AU, BR, CA, CN, CZ, EE, FI, HU, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: HYDROXAMIC ACID AND AMINO ACID DERIVATIVES AND THEIR USE AS ANTI-ARTHRITIC AGENTS



(I)

(57) Abstract

The present invention relates to a class of novel hydroxamic acids and carbocyclic acids and derivatives thereof that inhibit stromelysin, and are therefore useful for the treatment of arthritis. The class of compounds useful in this method of treatment is represented by Formula (I).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

TITLE

HYDROXAMIC ACID AND AMINO ACID DERIVATIVES AND THEIR USE AS ANTI-ARTHRITIC AGENTS

CROSS-REFERENCE TO EARLIER FILED APPLICATION

This application is a continuation-in-part of DM-6717, U.S. Serial Number 08/234,195 filed on April 28, 1994.

FIELD OF THE INVENTION

The present invention relates to small molecules which inhibit matrix metalloproteinases and/or the production of tumor necrosis factor (TNF), pharmaceutical preparations containing them and to their use as pharmaceutical agents.

BACKGROUND OF THE INVENTION

There is now a body of evidence that stromelysin (MMP-3) and other metalloproteinases (MMP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMP (tissue inhibitor of matrix metalloproteinase), which form inactive complexes with the MMP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A, 1970, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteinases. The available evidence supports that it is the metalloproteinases which are responsible for the degradation of the extracellular matrix of articullar cartillage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, immunohistochemical studies (Okada et al. Ann. Rheum. 48, 1989, 645) have demonstrated that stromelysin is synthesized and secreted by synovial lining cells in RA. Also, higher than normal levels of stromelysin in chondrocytes was detected in 90% of OA cartilage where stromelysin staining correlated with histological scores of pathology and with proteoglycan depletion (Okada et al. Lab Invest. 66, 1992, 680).

Therefore stromelysin, a matrix metalloproteinase (MMP-3), has been implicated as one of the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MMP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as stromelysin, collagenase, and gelatinase are potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis, invasion and growth.

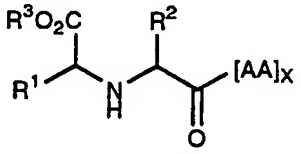
Tumour necrosis factor (TNF or TNF-α) is a cytokine which is produced initially as a cell-associated 28kD precusor. It is released as an active, 17kD form, which can mediate a large number of deleterious effects in *vivo*. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation, similar to those seen during acute infections and shock states.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumours.

Compounds which inhibit the production or action of TNF are therefore potentially useful for the treatment or prophylaxis of many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, crohn's disease, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage, and hyperoxic alveolar injury.

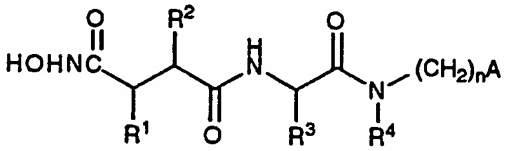
Since excessive TNF production has been noted in several diseases or conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may have particular advantages in the treatment or prophylaxis of diseases or conditions in which both mechanisms are involved.

PCT International Publication No. WO 92/213260 describes N-carboxyalkylpeptidyl compounds of general formula:

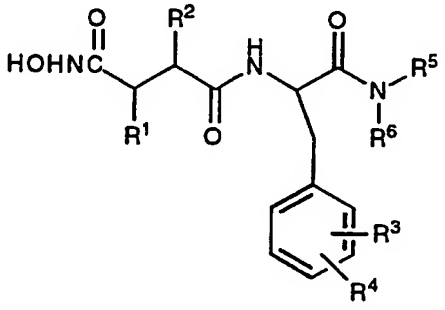


wherein AA is an amino acid, as inhibitors of matrix metallproteinase mediated diseases.

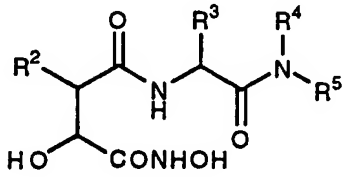
PCT International Publication No. WO 90/05716 discloses hydroxamic acid based collagenase inhibitors having the general formula:



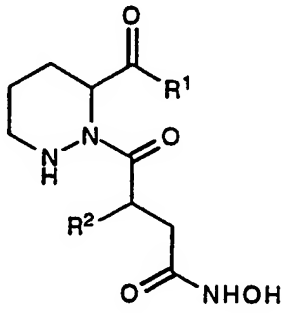
PCT International Publication No. WO 92/13831 describes related hydroxamic acids having collagenase inhibiting activity with the general formula:



PCT International Publication No. WO 94/02446 discloses metalloproteinase inhibitors which are natural amino acid derivatives of general formula:

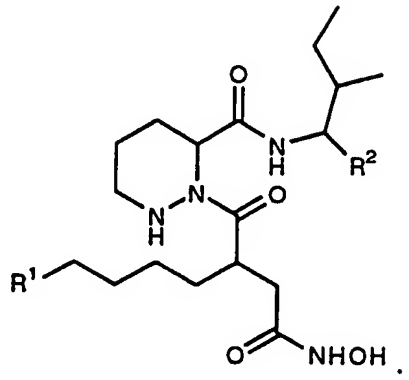


PCT International Publication No. WO 93/09097 discloses piperazinic acid derivatives of general formula:

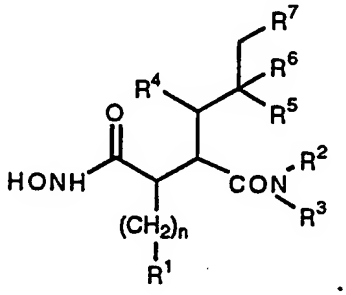


having inhibiting activity against type IV collagenase useful as a cancer metastasis suppressants.

Ogita et al. (J. Anti. 1992, 45, 1723-1732) report the isolation of a structurally related class of microbial metabolites, the matlystatins, which were identified through screening for inhibitors of Type IV collagenases and share the general formula shown below.



European Patent Application Publication No. 574,758 A1, discloses hydroxamic acid derivatives as collagenase inhibitors having the general formula:

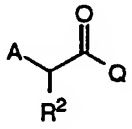


The compounds of the current invention act as inhibitors of stromelysin and other matrix metalloproteinases, thereby preventing cartilage loss and destruction. In addition, the compounds of the current invention inhibit the production of TNF, a cytokine implicated in inflammatory diseases. The hydroxamic and carboxylic acids and derivatives thereof of the present invention have been further found to be orally bioavailable. A number of the compounds reported to be inhibitors of metalloproteinases, such as collagenase, have suffered from lack of adequate bioavailability and are thus not useful as therapeutic agents, particularly if oral administration is desired. Poor oral activity has been ascribed to relatively high molecular weight, to inadequate solubility properties,

and to the presence of peptide bonds, which are vulnerable to cleavage by mammalian proteases in vivo and which generally cause the molecules to be extensively bound in human serum. The hydroxamic and carboxylic acids and derivatives described herein have a distinct advantage in this regard, in that they do not contain readily cleavable peptide bonds, are of low molecular weight, and can be hydrophilic yet still inhibit matrix metalloproteinases.

SUMMARY OF THE INVENTION

The present invention relates to a class of novel hydroxamic acids and carbocyclic acids and derivatives thereof that inhibit stromelysin and other matrix metalloproteinases, and also inhibit the production of tumor necrosis factor (TNF), and are therefore useful for the treatment of arthritis and other related inflammatory diseases. The class of compounds useful in this method of treatment is represented by Formula I below:



Formula I

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

A is selected from $-N(R^8)CH(R^9)CO_2H$ or $-CH(R^{11})C(R^{9a})(R^9)CO_2H$, $-C(R^1)(R^{1a})CONHOH$;

Q is selected from:

a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or

a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^1 is selected from:

H, halogen

C_1-C_{10} alkyl substituted with 0-3 R^4,

C_2-C_{10} alkenyl substituted with 0-3 R^4,

C_2-C_{10} alkynyl substituted with 0-3 R^4,

C_6-C_{10} aryl,

C_3-C_6 cycloalkyl, or

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, piperidinyl, pyrimidinyl or pyridazinyl, pyrrolidinyl, triazolidinyl, oxadiazolidinyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{1a} is selected from H, R^1, $NR^{10}R^{10a}$, OR^{17} or $S(O)_mR^{17}$

Alternately R^1 and R^{1a} can be taken together to form a 3-7 membered carbocyclic or a 5-7 membered, saturated heterocyclic ring, said heterocyclic ring containing 1-2 heteroatoms selected from N, O, and S, and optionally substituted at carbon with keto;

R^2 is selected from:

C_2-C_{10} alkyl substituted with 0-3 R^{17b},

$(-CH_2)_nO-(C_1-C_8$ alkyl$)-R^{20}$, or

$(-CH_2)_nS-(C_1-C_8$ alkyl$)-R^{20}$,

$-(CH_2)_nOR^{20}$,

$-(CH_2)_nSR^{20}$,
$-(CH_2)_nS-(C_1-C_6)$ alkyl, or
$-(CH_2)_nO-(C_1-C_6)$ alkyl;

n=0-8

R^3 is selected from: OR^{11}, $NHCH(R^{12})COR^{13}$, $NHCH(R^{12})COOR^{11}$, $NHCH(R^{12})CONR^{14}R^{15}$, $NR^{10}R^{10a}$;

R^4 is selected from:
$-OR^{17a}$, $-SO_mR^{17a}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{18};

m=0-2;

R^{4a} is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_1-C_4 alkylcarbonyl,
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl,

thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^5 and R^6 are independently selected from:
hydrogen,
hydroxy,
C_1-C_6 alkyl substituted with 0-3 R^{20},
phenyl,
C_7-C_{14} arylalkyl,
C_7-C_{14} arylalkoxy,
C_1-C_4 alkylcarbonyl,
C_7-C_{14} arylalkoxycarbonyl,
C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$,
C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$,
C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$,
=O, =S, or a ketal or thioketal form thereof when R^5 or R^6 are attached to a saturated carbon atom, or = O when R^5 or R^6 is attached to sulfur;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein said heterocyclic ring contains one or two N, O or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,

alkoxycarbonyl,
arylalkoxycarbonyl,
alkylaminocarbonyl,
arylsulfonyl,
heteroarylalkoxycarbonyl,
cycloalkoxycarbonyl,
heteroarylsulfonyl,
alkyesulfonyl,
cycloalkylsulfonyl,

R^9 is selected from:
H,
C_1-C_8 alkyl substituted with 0-3 R^{4a},
C_2-C_8 alkenyl substituted with 0-3 R^{4a},
C_2-C_8 alkynyl substituted with 0-3 R^{4a};

R^{9a} is selected from H, OR^{17}, SR^{17} or NR^{10} R^{10a},

Alternately R^9 and R^{9a} can be taken together to form a 3-7 membered carbocyclic or heterocyclic ring, said heterocyclic ring containing 1-2 heteroatoms selected from N, O or S, optionally substituted on carbon with keto;

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4 or
C_1-C_6 alkylcarbonyl;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,
C_1-C_4 alkyl substituted with 0-3 R^4,
C_2-C_4 alkenyl substituted with 0-3 R^4,
C_2-C_4 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{17A}
C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
H,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, isothiazolyl, thiazolinyl,
thiazolidinyl, isothiazolinyl, piperidinyl,
pyrimidinyl, pyridazinyl, pyrazinyl,
pyrrolidinyl, pyrrolyl, N-methylpyrrolyl,
triazolyl, triazolidinyl, oxazolyl,
isoxazolyl, oxazolinyl, isoxazolinyl,
oxazolidinyl, oxadiazolyl, oxadiazolidinyl,
imidazolyl, imidazolidinyl, said heterocyclic
ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:
phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano,
C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide,
C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$,
$-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy,
ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4
haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4
alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4
alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,
phenyl, optionally substituted with halogen, C_1-C_4
alkyl, C_1-cyalkoxy, hydroxy, or $-NR^{10}R^{10a}$,
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, isothiazolyl, thiazolinyl,
thiazolidinyl, isothiazolinyl, piperidinyl,
pyrimidinyl, pyridazinyl, pyrazinyl,
pyrrolidinyl, pyrrolyl, N-methylpyrrolyl,
triazolyl, triazolidinyl, oxazolyl,
isoxazolyl, oxazolinyl, isoxazolinyl,
oxazolidinyl, oxadiazolyl, oxadiazolidinyl,

imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$, =O or =S when attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl,

isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$;

R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl; and

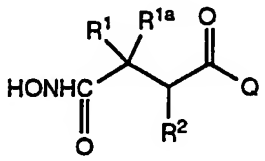
R^{20} is selected from:

aryl substituted with 0-5 R^{18},

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

One embodiment of the present invention relates to a novel class of compounds embodied within the class of compounds of Formula I and to pharmaceutical

compositions and methods of use of these novel compounds for the inhibition of stromelysin and other matrix metalloproteinases, for the inhibition of the production of tumor necrosis factor (TNF) and in the treatment of Osteo and Rheumatoid Arthritis (OA and RA). These novel compounds are represented by Formula II below:



Formula II

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

Q is selected from:

a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or

a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^1 is selected from:

H, halogen

C_1-C_{10} alkyl substituted with 0-3 R^4,

C_2-C_{10} alkenyl substituted with 0-3 R^4,

C_2-C_{10} alkynyl substituted with 0-3 R^4,

C_6-C_{10} aryl,

C_3-C_6 cycloalkyl, or

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl,

thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{1a} is selected from H, $NR^{10}R^{10a}$, OR^{17} or $S(O)_mR^{17}$

Alternately R^1 and R^{1a} can be taken together to form a 3-7 membered carbocyclic or heterocyclic ring, said heterocyclic ring containing 1-2 hetero-atoms selected from N, O, and S;

R^2 is selected from:
C_2-C_{10} alkyl substituted with 0-3 R^{17b},
$(-CH_2)_nO-(C_1-C_8$ alkyl$)-R^{20}$, or
$(-CH_2)_nS-(C_1-C_8$ alkyl$)-R^{20}$,
$-(CH_2)_nOR^{20}$,
$-(CH_2)_nSR^{20}$,
$-(CH_2)_nS-(C_1-C_6)$ alkyl, or
$-(CH_2)_nO-(C_1-C_6)$ alkyl;

n=0-6

R^3 is $-NR^{10}R^{10a}$

R^4 is selected from:
OR^{17}, SO_mR^{17}, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

m=0-2;

R^5 and R^6 are independently selected from:
hydrogen, hydroxy, C_1-C_6 alkyl substituted with 0-3 R^{20}, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, C_7-C_{14} arylalkoxycarbonyl, C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$, C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$, C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein the heterocyclic ring contains one to two N, O, or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
arylsulfonyl,

heteroarylsulfonyl,
cycloakoxycarbonyl,
keteroarylalkoxycarbonyl,
alkylsulfonyl, or
cycloalkylsulfonyl;

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,
C_1-C_4 alkyl substituted with 0-3 R^4,
C_2-C_4 alkenyl substituted with 0-3 R^4,
C_2-C_4 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{17A}
C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
H,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:
phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide,

C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

phenyl, optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or $NR^{10}R^{10a}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted on the aliphatic carbons with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$ =O or =S when attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

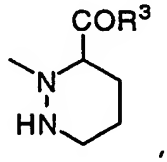
or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$;

R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{20} is selected from:
aryl substituted with 0-5 R^{18},
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

with the following proviso:
when R^1 and R^{1a} are both hydrogen and Q is



then R^2 is not hydrogen, C_3-C_{10} alkyl or (C_1-C_4 alkyl)aryl.

Presently, preferred compounds of this embodiment are compounds of Formula II wherein:

Q is a 5-7 membered saturated heterocyclic ring system containing at least one nitrogen and optionally containing an additional heteroatom selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or -C(=O)R^3;

R^1 is selected from:
H,

C_1-C_4 alkyl substituted with 0-3 R^4;

R^2 is selected from:
C_2-C_4 alkyl substituted with 0-3 R^{17b},
-O-(C_1-C_6 alkyl)-R^{20},
-S-(C_1-C_6 alkyl)-R^{20},
-CH_2O-(C_1-C_5 alkyl)-R^{20}, or
-CH_2S-(C_1-C_5 alkyl)-R^{20};

R^8 is hydrogen;

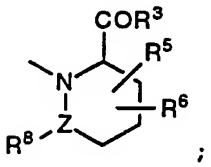
R^{10} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-4 R^4;

Presently more preferred compounds of this embodiment are compounds of Formula II wherein:

Q is a heterocycle selected from hexahydro-1-pyridazinyl, 2-tetrahydro-1,2-oxazinyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methylpiperazinyl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl-1-oxide, tetrahydro-1,4-thiazin-4-yl-1,1-dioxide, 1-oxa-2-piperidinyl, said heterocycle being substituted with 0-3 groups selected from -C(=O)R^3, R^5, R^6, or R^8.

Still more preferred compounds of this embodiment are compounds of Formula II wherein:

Q is



;

Z is N or O;

R^5 is selected from:
hydrogen, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, or C_7-C_{14} arylalkoxycarbonyl; and

R^6 is hydrogen;

with the proviso that R^8 is absent when Z is O.

Specifically preferred compounds of this embodiment are selected from:
[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-(methylthio-2-thienyl)succinyl]-N^1-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

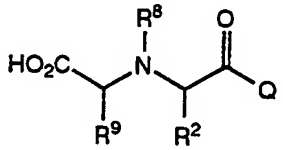
[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-4'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-5'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-6'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-[5',6']benzopiperazic acid-N-methyl amide,

A second embodiment of the present invention relates to a class of novel compounds also embodied within the class of compounds of Formula I and to pharmaceutical compositions and methods of use of these novel compounds for the inhibition of stromelysin and other matrix metalloproteinases, for the inhibition of the production of tumor necrosis factor (TNF) and in the treatment of Osteo and Rheumatoid Arthritis (OA and RA) and related diseases. These compounds are represented by Formula III below:



Formula III

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

Q is selected from:

a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or

a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^2 is selected from

C_1-C_8 alkyl substituted with 0-3 R^{17b},
C_1-C_8 alkenyl substituted with 0-3 R^{17b},
C_1-C_8 alkynyl substituted with 0-3 R^{17b},
$-(CH2)_n-O-(C_1-C_8$ alkyl),
$-(CH2)_n-S-(C_1-C_8$ alkyl),
$-(CH_2)_nO-(C_1-C_8$ alkylene)$-R^{20}$,
$(CH_2)_nS$(C1-C8 alkylene)$-R^{20}$
$-(CH_2)_nOR^{20}$, or
$-CH_2)_nSR^{20}$

n=1-8

R^3 is $NR^{10}R^{10a}$;

R^4 is selected from:

$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, piperidinyl, pyrimidinyl or pyridazinyl, said heterocyclic ring system being substituted with 0-2 R^{19};

m= 0-2;

R^{4a} is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^5 and R^6 are independently selected from:
hydrogen, hydroxy, C_1-C_6 alkyl substituted with 0-3 R^{20}, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, C_7-C_{14} arylalkoxycarbonyl, C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$, C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$, C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$, =0, =S, or a ketal or thioketal form thereof when R^5 or R^6 are attached to a saturated carbon atom, or = 0 when R^5 or R^6 is attached to sulfur;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein the heterocyclic ring contains one or two N, O or S

atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
alkylaminocarbonyl,
arylsulfonyl,
heteroarylsulfonyl,
cycloakoxycarbonyl,
keteroarylalkoxycarbonyl,
alkylsulfonyl, or
cycloalkylsulfonyl;

R^9 is selected from:
H,
C_1-C_5 alkyl substituted with 0-3 R^{4a},
C_2-C_5 alkenyl substituted with 0-3 R^{4a},
C_2-C_5 alkynyl substituted with 0-3 R^{4a};

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,

C_1-C_8 alkyl substituted with 0-3 R^4,
C_2-C_8 alkenyl substituted with 0-3 R^4,
C_2-C_8 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{17A}
C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

phenyl, optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or $NR^{10}R^{10a}$;

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused

5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted on the aliphatic carbons with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$, =O or =S when attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$; or,

R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{20} is selected from:

aryl substituted with 0-5 R^{18},

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

Preferred compounds of the second embodiment are compounds of Formula III wherein:

Q is a heterocycle selected from hexahydro-1-pyridazinyl, 2-tetrahydro-1,2-oxazinyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methylpiperazinyl, tetrahydro-1,4-

thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl-1-oxide, tetrahydro-1,4-thiazin-4-yl-1,1-dioxide, said heterocycle being substituted with 0-3 groups selected from $-C(=O)R^3$, R^5, R^6, or R^8;

R^2 is selected from
C_2-C_4 alkyl substituted with 0-3 R^{17b}
$-(CH_2)_nO-(C_1-C_5$ alkyl$)-R^{20}$, or
$-(CH_2)_nS-(C_1-C_5$ alkyl$)-R^{20}$;

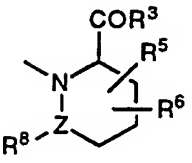
n= 1-5;

R^8 is hydrogen;

R^9 is selected from:
hydrogen,
C_1-C_5 alkyl substituted with 0-3 R^{4a};

More preferred compounds of the second embodiment are compounds of Formula III wherein:

Q is



Z is N or O;

with the proviso that R^8 is absent when Z is O.

Specifically preferred compounds of the second embodiment are selected from:
N-[1(R)-carboxy-ethyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyl]-α-(S)-heptylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyl]-α-(S)-octylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyl]-α-(S)-ethylphenylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyl]-α-(S)-propylphenylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethylthiobenzyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethylthiobenzyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethylthiobenzyl]-α-(S)-ethylphenyl-glycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethylthiobenzyl]-α-(S)-propylphenyl-glycine-(S)-N^2-piperazic acid methyl amide.

N-[1(R)-carboxy-ethyloxybenzyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyloxybenzyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide,

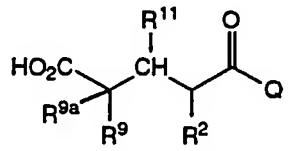
N-[1(R)-carboxy-ethyloxybenzyl]-α-(S)-ethylphenyl-glycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-ethyloxybenzyl]-α-(S)-propylphenyl-glycine-(S)-N^2-piperazic acid methyl amide,

N-[1(R)-carboxy-4-(*p*-toluenesulfonyl)butyl]-α-(S)-phenethylglycyl-(S)-N^2-piperazic acid methyl amide, and

N-[1(R)-carboxyethyl]-α-[2-(4-phenylphenoxy)ethyl]-glycyl-(S)-N^2-piperazic acid methyl amide.

A third embodiment of the present invention relates to a class of novel compounds also embodied within the class of compounds of Formula I and to pharmaceutical compositions and methods of use of these novel compounds for the inhibition of stromelysin and other matrix metalloproteinases, for the inhibition of the production of tumor necrosis factor (TNF) and in the treatment of Osteo and Rheumatoid Arthritis (OA and RA) and related diseases. These compounds are represented by Formula IV below:



Formula IV

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

Q is selected from:

a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or

a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^2 is selected from

C_1-C_6 alkyl substituted with 0-3 R^{17b},

$-(CH2)_n-O-(C_1-C_8$ alkyl),

$-(CH2)_n-S-(C_1-C_8$ alkyl),

$-(CH_2)_nO-(C_1-C_8$ alkylene)$-R^{20}$,

$(CH_2)_nS$(C1-C8 alkylene)$-R^{20}$

$-(CH_2)_nOR^{20}$, or

$-CH_2)_nSR^{20}$

n=0-8

R^3 is $NR^{10}R^{10a}$;

R^4 is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, piperidinyl, pyrimidinyl or
pyridazinyl, said heterocyclic ring system
being substituted with 0-2 R^{19};

R^{4a} is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, isothiazolyl, thiazolinyl,
thiazolidinyl, isothiazolinyl, piperidinyl,
pyrimidinyl, pyridazinyl, pyrazinyl,
pyrrolidinyl, pyrrolyl, N-methylpyrrolyl,
triazolyl, triazolidinyl, oxazolyl,
isoxazolyl, oxazolinyl, isoxazolinyl,
oxazolidinyl, oxadiazolyl, oxadiazolidinyl,
imidazolyl, imidazolidinyl, said heterocyclic
ring system being substituted with 0-5 R^{19};

R^5 and R^6 are independently selected from:
hydrogen, hydroxy, C_1-C_6 alkyl substituted with 0-3 R^{20}, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, C_7-C_{14} arylalkoxycarbonyl, C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$, C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$, C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$, =O, =S, or a ketal or thioketal form thereof when R^5 or R^6 are attached to a saturated carbon atom, or = O when R^5 or R^6 is attached to sulfur;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein the heterocyclic ring contains one or two N, O or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
alkylaminocarbonyl,
arylsulfonyl,
heteroarylsulfonyl,
cycloakoxycarbonyl,
keteroarylalkoxycarbonyl,
alkylsulfonyl, or
cycloalkylsulfonyl;

R^9 is selected from:
H,
C_1-C_6 alkyl substituted with 0-3 R^{4a},
C_2-C_6 alkenyl substituted with 0-3 R^{4a},

C_2-C_6 alkynyl substituted with 0-3 R^{4a};

R^{9a} is selected from H, OR^{17}, $NR^{10}R^{10a}$ or $S(O)_nR^{17}$,

Alternately R^9 and R^{9a} can be taken together to form a 3-7 membered carbocyclic or heterocyclic ring said heterocyclic ring containing 1-2 heteroatoms selected from N, O or S;

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,
C_1-C_8 alkyl substituted with 0-3 R^4,
C_2-C_8 alkenyl substituted with 0-3 R^4,
C_2-C_8 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{17A}

C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$, phenyl, optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or $NR^{10}R^{10a}$;

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted on the aliphatic carbons with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$, =O or =S when attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-

C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$; or,

R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-

C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{20} is selected from:

aryl substituted with 0-5 R^{18},

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

Preferred compounds of the third embodiment are compounds of Formula IV wherein:

Q is a heterocycle selected from hexahydro-1-pyridazinyl, 2-tetrahydro-1,2-oxazinyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methylpiperazinyl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl-1-oxide, tetrahydro-1,4-thiazin-4-yl-1,1-dioxide, said heterocycle being substituted with 0-3 groups selected from $-C(=O)R^3$, R^5, R^6, or R^8;

R^2 is selected from

C_2-C_4 alkyl substituted with 0-3 R^{17b}

$-(CH_2)_nO-(C_1-C_5$ alkyl$)-R^{20}$, or

$-(CH_2)_nS-(C_1-C_5$ alkyl$)-R^{20}$;

n= 0-6;

R^8 is hydrogen;

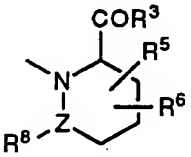
R^9 is selected from:

hydrogen,

C_1-C_4 alkyl substituted with 0-3 R^{4a};

More preferred compounds of the third embodiment are compounds of Formula IV wherein:

Q is



Z is N or O;

with the proviso that R^8 is absent when Z is O.

Specifically preferred compounds of the third embodiment are compounds selected from the group consisting of:

2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(1,1'-biphenyl)yl]propyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-(4-propylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-(4-butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-(4-t-butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(4-fluorophenyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(4-fluorophenyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-2-n-octyl-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine.

2-[2(R)-[2-[(4-thiazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-thiazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-thiazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-thiazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-oxazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-oxazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-oxazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-oxazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(dimethylamino)methylphenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(dimethylamino)methylphenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(dimethylamino)methylphenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[4-(dimethylamino)methylphenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

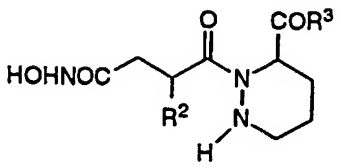
2-[2(R)-[2-[(4-imidazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-imidazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine,

2-[2(R)-[2-[(4-imidazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine, and

2-[2(R)-[2-[(4-imidazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine.

A fourth embodiment of the invention provides compounds of formula IIa or pharmaceutically acceptable salts or prodrug forms thereof which are useful in the method of treating Osteo and Rheumatoid arthritis (OA and RA) and related inflammatory diseases which uses a stromelysin or related matrix metalloproteinase inhibitor as a cartilage protecting agent:



Formula IIa

wherein:

R^2 is selected from:
H,
C_3-C_{10} alkyl, or
aryl-(C_1-C_4 alkyl)-;

R^3 is selected from OR^{11}, $NHCH(R^{12})COR^{13}$, $NR^{10}R^{10a}$, $NHCH(R^{12})COOR^{11}$, or $NHCH(R^{12})CONR^{14}R^{15}$;

R^{10} and R^{10a} are each independently selected from hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R^{11}, R^{12}, and R^{15} are each independently selected from hydrogen or C_1-C_4 alkyl;

R^{13} and R^{14} are C_1-C_4 alkyl.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention it has been discovered that the compounds above are useful as inhibitors of stromelysin and similar matrix metalloproteinases, and the production of TNG and for the treatment of rheumatoid arthritis, osteoarthritis and similar pathological conditions.

The present invention also provides methods for the treatment of osteo- and rheumatoid arthritis and other related inflammatory diseases by administering to a host a pharmaceutically or therapeutically effective or

acceptable amount of a compound of formula (I) as described above. By therapeutically effective amount, it is meant an amount of a compound of the present invention effective to inhibit stromelysin or related matrix metalloproteinases and the production of TNF or to treat the symptoms of osteo- or rheumatoid arthritis or related inflammatory diseases in a host.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents. Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

By "therapeutically effective amount" it is meant an amount of a compound of Formula I that when administered alone or in combination with an additional therapeutic agent to a cell or mammal is effective to inhibit stromelysin so as to prevent or ameliorate the inflamatory disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in

the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention may contain asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (for example R^1 through R^{20}, R^{10a}, n, m, Z, X, etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^{17}, then said group may optionally be substituted with up to three R^{17} and R^{17} at each occurrence is selected independently from the defined list of possible R^{17}.

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring.

When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of Formula I, then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, said piperazinyl, piperidinyl, tetrazolyl group may be bonded to the rest of the compound of Formula I via any atom in such piperazinyl, piperidinyl, tetrazolyl group.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to

survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (for example, "C_1-C_{10}" denotes alkyl having 1 to 10 carbon atoms); "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or polycyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds

which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

"Alkylcarbonyl" is intended to include an alkyl group of an indicated number of carbon atoms attached through a carbonyl group to the residue of the compound at the designated location. "Alkylcarbonylamino" is intended to include an alkyl group of an indicated number of carbon atoms attached through a carbonyl group to an amino bridge, where the bridge is attached to the residue of the compound at the designated location. "Alkylcarbonyloxy" is intended to include an alkyl group of an indicated number of carbon atoms attached to a carbonyl group, where the carbonyl group is attached through an oxygen atom to the residue of the compound at the designated location.

The terms "alkylene", "alkenylene", "phenylene", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of Formula I. Such "alkylene", "alkenylene", "phenylene", and the like, may alternatively and equivalently be denoted herein as "-(alkyl)-", "-(alkyenyl)-" and "-(phenyl)-", and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl; the term "arylalkyl" represents an aryl group attached through an alkyl bridge.

As used herein, "carbocycle" or "carbocyclic residue" or "carbocyclic ring system" is intended to mean any stable 3- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or up to 26-membered polycyclic carbon ring, any of which may be

saturated, partially unsaturated, or aromatic. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heteroaryl" or "heterocyclic" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6*H*-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, thiophenyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl,

indolyl, 1*H*-indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazole, carbazole, ß-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, hexahydropyridazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids, modified and unusual amino acids, as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids,such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, ornithine, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid,

1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The term "amino acid residue" as used herein means that portion of an amino acid (as defined herein) that is present in a peptide.

The term "peptide" as used herein means a compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. The term "peptide" also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptide mimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

The term "peptide bond" means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of Formula I is modified by making acid or base salts of the compound of Formula I. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula I are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are

bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, phosphate esters, dimethylglycine esters, aminoalkylbenzyl esters, aminoalkyl esters and carboxyalkyl esters of alcohol and phenol functional groups in the compounds of formula (I); and the like.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an

organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

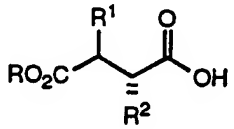
Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of Formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all

proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the educt molecule must be compatible with the reagents and reactions proposed. Not all compounds of Formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

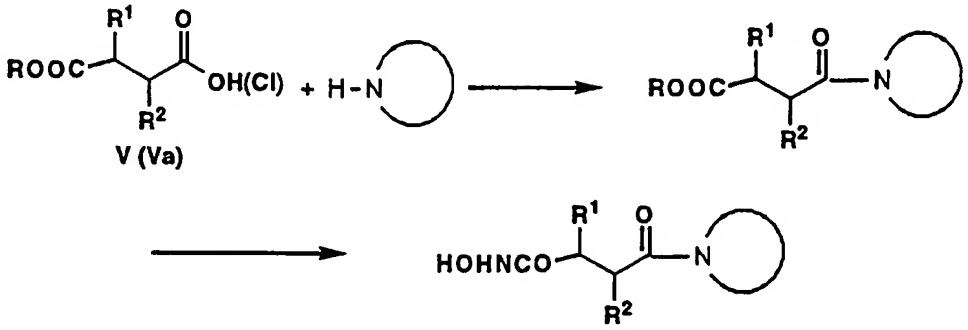
Compounds of formula I wherein A is HONHCOCH(R^1) and Q is a saturated N-heterocycle linked via a N atom in the ring are prepared by condensation of acids of formula (V):



V

wherein R is an ester protecting group, and R^1 and R^2 are defined as provided in the preceding Summary of the Invention in connection with formula I, with an appropriately substituted N-heterocycle to form an amide bond between the carbonyl of (V) and a basic nitrogen in the ring of said heterocycle as shown in Scheme 1.

SCHEME 1

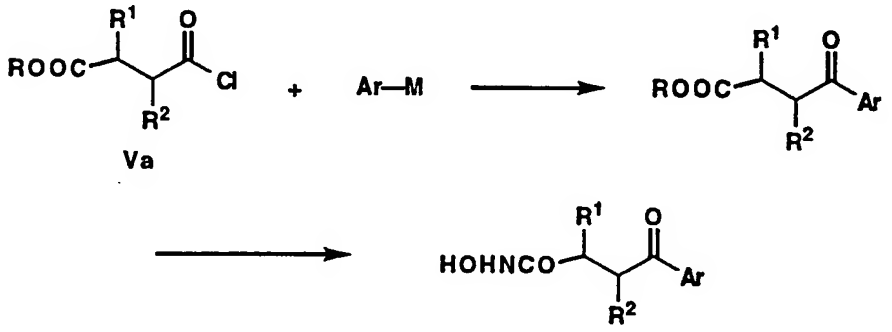


The condensation is carried out using any of the many methods for the formation of amide bonds known to one skilled in the art of organic synthesis. These methods include but are not limited to conversion of acid (V) to the corresponding acid chloride (Va), or use of standard coupling procedures such as the azide method, mixed carbonic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimides) method, active ester (p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, carbonyldiimidazole method, phosphorus reagents such as BOP-Cl. Some of these methods (especially the carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole. The preferred method is treatment of the cyclic amine with the acid chloride prepared from (V). Methods for conversion of carboxylic acids to acid chlorides are described in (J. March, Adv. Org. Chem. 1985, p. 1146, J. Wiley & Son, USA) and include, for example, treatment of the acid with oxalyl chloride in the presence of a catalytic amount of N,N'-dimethylformamide. Removal of the ester protecting group followed by activation the resulting acid, for example with isobutylchloroformate, and reaction with O-

benzylhydroxylamine gives a protected hydroxamic acid. Deprotection gives the hydroxamic acid.

Compounds of Formula I wherein A is HONHCOCH(R^1) and Q is aryl or heteroaryl are prepared by treatment of the acid chloride (Va) prepared from acid (V) with a metallated aryl or heteroaryl as shown in Scheme 2, where R, R^1 and R^2 are defined as above, Ar represents an aryl or heteroaryl group and M is lithium, magnesium bromide or trialkyl or triaryltin. The organometallic species, Ar—M, are obtained by treatment of an aryl or heteroaryliodide or bromide with an alkyl or aryl lithium reagent, magnesium or a trialkyltin reagent to give the corresponding lithium, magnesium bromide or tin species using methods well known to one skilled in the art. The condensation of a trialkyltin species with acid chlorides in the presence of a catalytic amount of a palladium(0) catalyst has been reviewed by Stille (Angew. Chem. Int. Ed. Engl., **1986** 25:508). In cases where the heteroaryl species is sufficiently reactive, either direct metallation or direct condensation of the unactivated heteroaryl compound with the acid chloride is possible. (See B. Oddo, Gazz. Chim. Ital., **1911**, 41:234.) The intermediate ester is then converted to the target hydroxamic acid as described above.

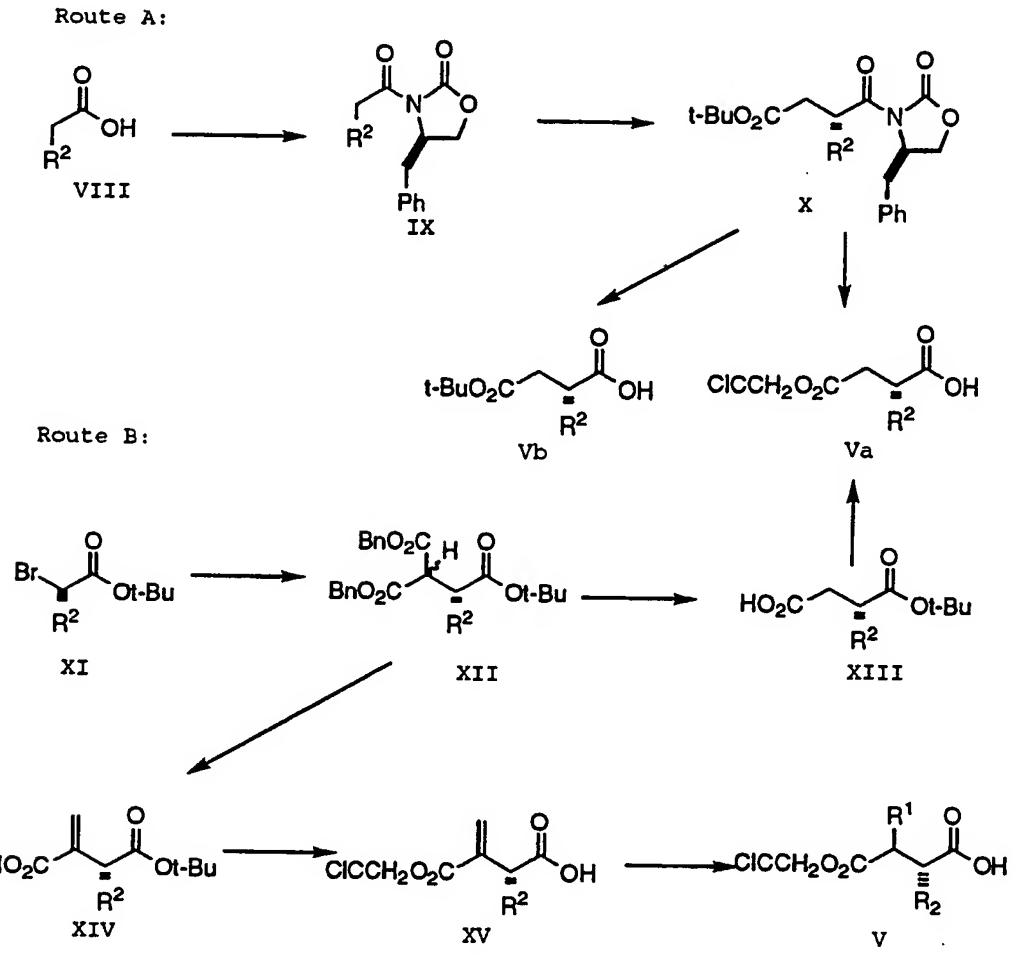
SCHEME 2



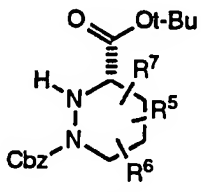
The acids of formula (V) are prepared as previously described (Crimmin et al Synlett **1993**, 137; Tamaki et al Tetrahedron Lett **1993**, 34:683) or by the general routes shown in Scheme 3. An appropriately substituted carboxylic acid (VIII) is converted to the chiral oxazolidinone (IX) by the method of Evans. Deprotonation with a strong base followed by treatment with t-butyl bromoacetate, produces intermediate (X). Transesterification of the chiral auxiliary with LiOBn, followed by acid treatment to remove the tert-butyl protecting group and conversion of the acid to the trichloroethylester gives a compound of formula (Va), where R^1 is hydrogen. Alternately, hydrolysis of the chiral auxilliary can be accomplished with alkaline hydrogen peroxide to give acid (Vb).

Alternately, as shown in Route B, an α-bromoester of formula (XI) is treated with the potassium salt of dibenzyl malonate to give triester (XII). Methods for the preparation of α-bromoesters of amino esters are well known to one skilled in the art of organic synthesis (R. S. Compagnone and H. Rapoport, J. Org. Chem. 1986, 51, 1713.) Removal of the benzyl esters and decarboxylation gives acid (XIII) which can be converted to (Va) by manipulation of the acid functions using standard methodology. Acids (V) where R^1 is other than hydrogen are obtained from intermediate (XII) via Mannich reaction followed by quaternization and elimination to give the methylene compound (XIV). Once again manipulation of the acid functions gives the desired mono-trichloroethylester. Simple reduction of the alkene gives (V) where R^1 is methyl. Compounds with R^1 other than hydrogen or methyl are obtained from intermediate (XIV) by 1,4-addition of appropriate nucleophiles to the α,β-unsaturated acid moiety. Suitable nucleophiles include, but are not limited to alkyllithiums, alkylmagnesium halides, thiols and alkoxides, and the like.

SCHEME 3



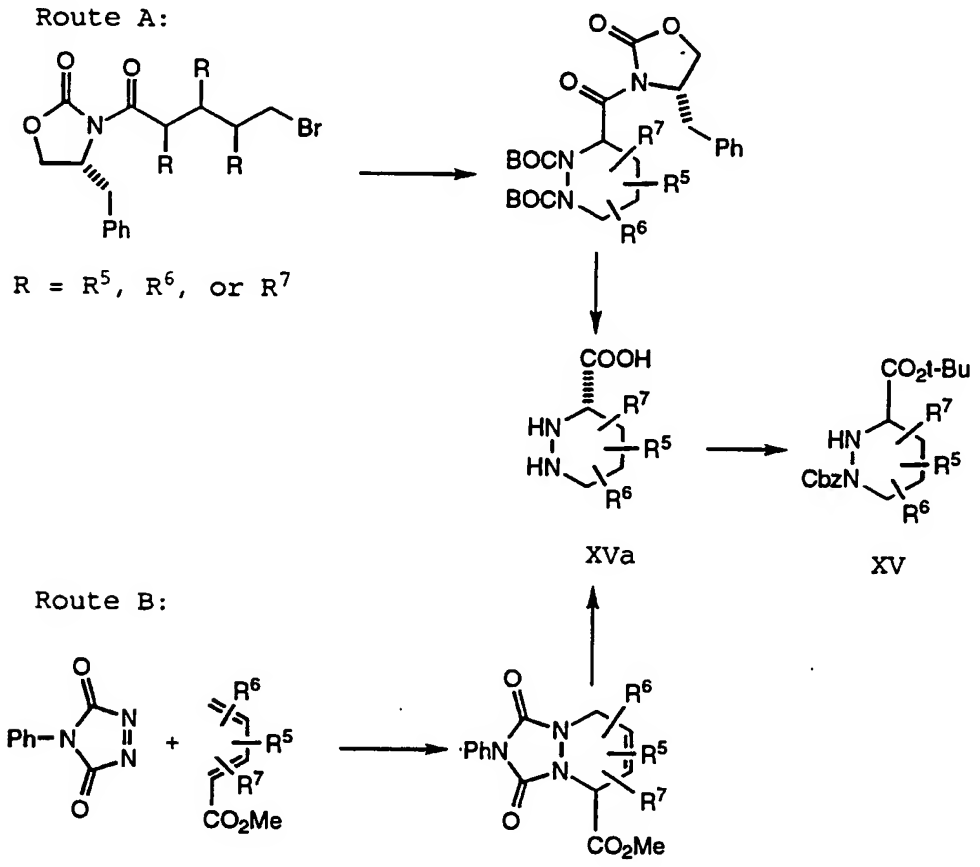
Compounds of formula II, wherein Z is N may be prepared from piperazic acid derivatives of formula (XV), wherein the designations R^5, R^6, R^7 are defined as provided in the preceding Summary of the Invention in connection with formula II.



(XV)

Unsubstituted piperazic acid esters of formula (XV) may be prepared as described by Adams et al. (Synth. Commun. 1988, 18, 2225) or by the general synthetic routes shown in Scheme 4.

Scheme 4

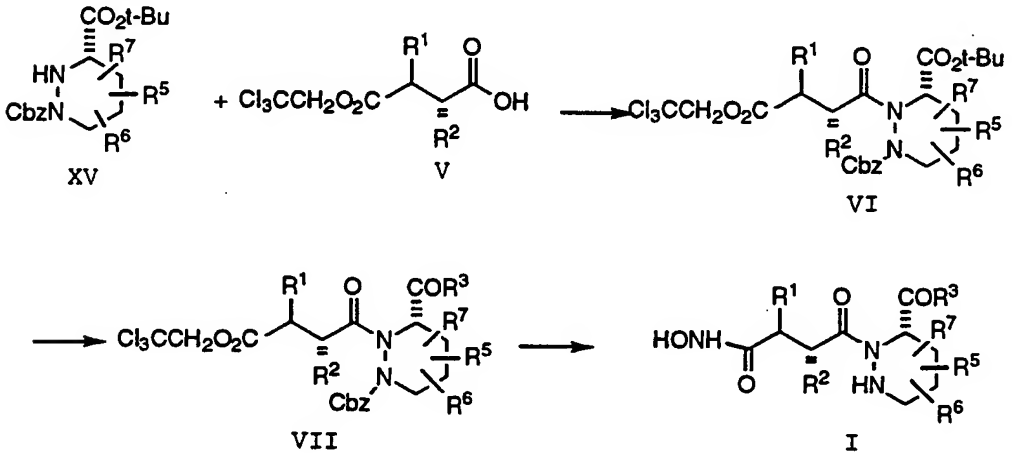


Asymmetric addition of di-t-butyl diazodicarboxylate to a chiral oxazolidinone prepared from an appropriately substituted 5-bromovaleric acid derivative (K. J. Hale, V. M. Delisser, and S. Manaviazar Tetrahedron Lett., 1992, 33, 7613.) followed by removal of the BOC groups and hydrolysis of the oxazolidinone gives the piperazic acid derivative (XVa).

Methods of choice for removal of the BOC groups are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane. Hydrolysis of the oxazolidinone is preferably carried out by treatment with aqueous lithium hydroxide. Compounds of formula (XVa) can be easily converted to a compound of formula (XV) by methods well known to one of ordinary skill in the art of organic synthesis, for example, by treatment with benzylchloroformate in the presence of a suitable base such as aqueous sodium hydroxide followed by exposure to isobutylene under acid catalysis.

In an alternate method for the preparation of compounds of formula (XV), Diels-Alder cyclization of 4-phenyl-1,2,4-triazoline-3,5-dione with an appropriately substituted diene (Adams, vide supra) yields an adduct which after reduction and alkaline hydrolysis gives piperazic acid derivatives (XVa) which are converted to (XV) as described above. Compounds of Formula II wherein Z is N and R^8 is H can be prepared from piperazic esters of formula (XV) and acids of formula (V) as outlined in Scheme 5.

Scheme 5



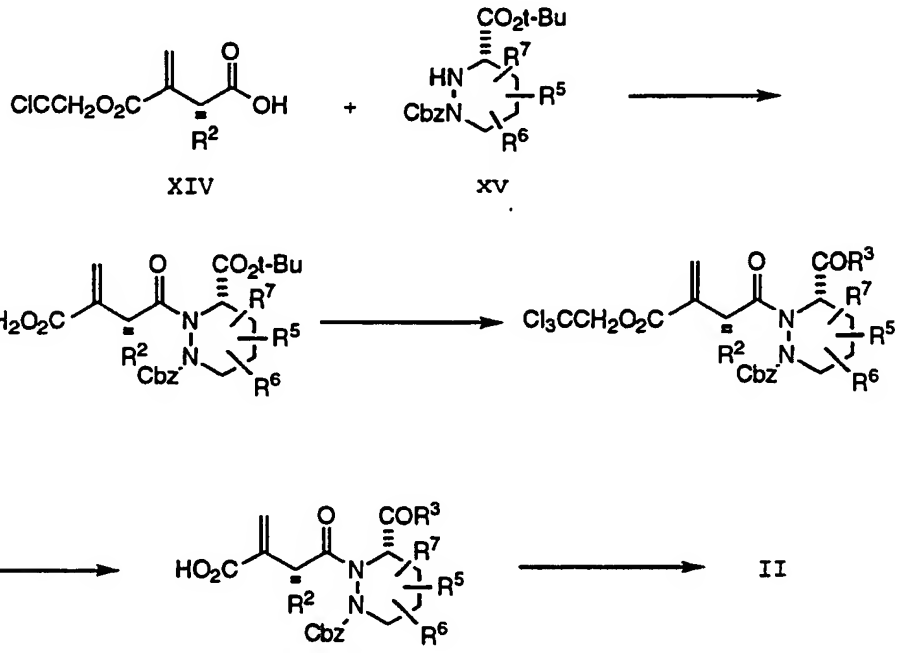
Piperazic esters (XV) are coupled with acids of formula (V) to give amides of formula (VI) as described above.

For compounds of Formula II wherein Z is N, and R^8 is H and R^3 is $-NR^{10}R^{10a}$, the synthesis proceeds by hydroxylsis of the t-butyl ester of a compound of Formula (VI), followed by activation of the resulting acid with a coupling reagent chosen from the list of standard procedures above, for example, isobutylchloroformate, and treatment with an excess of an amine of formula $R^{10}(R^{10a})NH$ or corresponding alcohol to give the corresponding amide. The trichloroethyl ester is removed by reduction followed by conversion to the hydroxamic acid as previously described. Tbe preferred methods for removal of the TCE ester are reduction with zinc dust or mild base hydrolysis. For removal of the benzyl and Cbz groups in one pot, the reagents of choice are hydrogenation conditions using hydrogen at atmospheric pressure or in a Parr apparatus at elevated hydrogen pressure, or cyclohexene or ammonium formate over palladium, palladium hydroxide on charcoal or platinum oxide in methanol, ethanol or tetrahydrofuran, or combination of these solvents (P. N. Rylander, Hydrogenation Methods, Academic Press, 1985). For compounds wherein R^1 contains sulfur, removal of the benzyl and Cbz protecting groups is carried out by hydrogenation in the presence of Wilkinson's catalyst or by treatment with trimethylsilyliodide.

An alternate route to compounds of Formula II wherein R^1 is other than hydrogen or methyl is depicted in Scheme 6. An acid of formula (XIV) is condensed with a compound of formula (XV) using one of the methods described above, to give (XVI). This intermediate is converted as described to acid (XVII). Michael addition of an appropriate nucleophile and conversion of the acid functionality to a hydroxamic acid gives compounds of formula II. This route can be used to prepare other

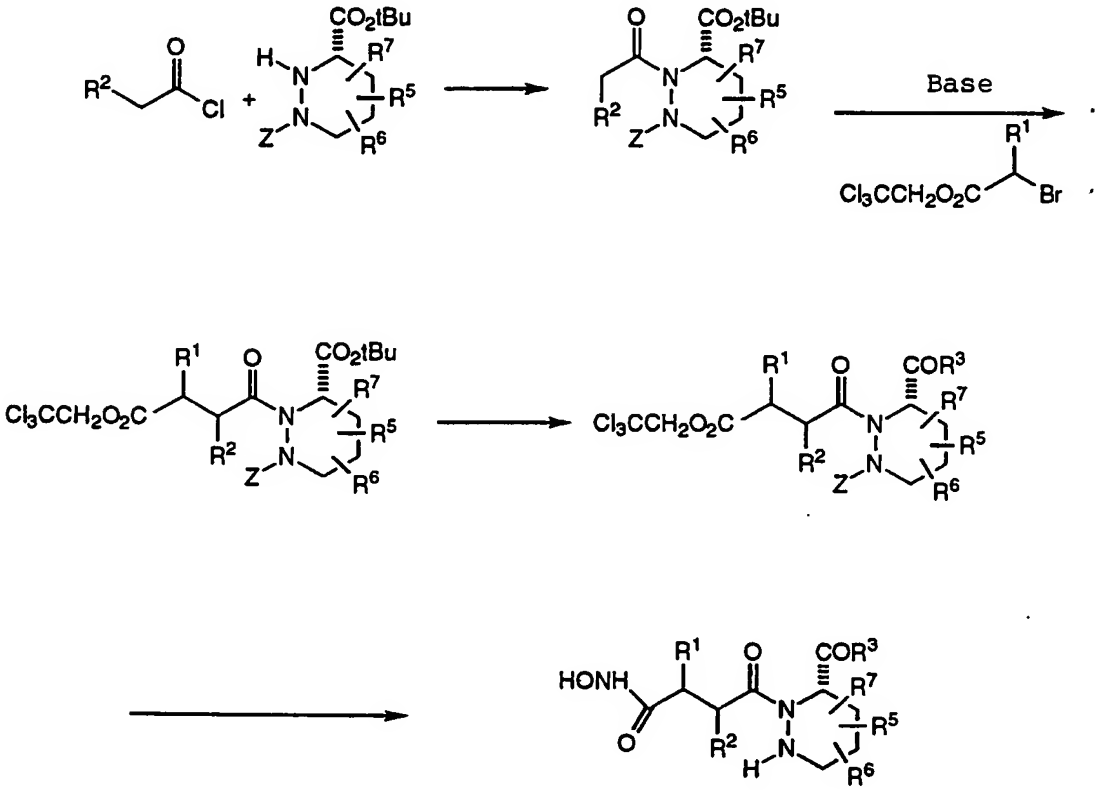
compounds of formula II by replacing compound (XV) in scheme 6 with the heterocycles, aryl and heteroaryl reagents described above

Scheme 6



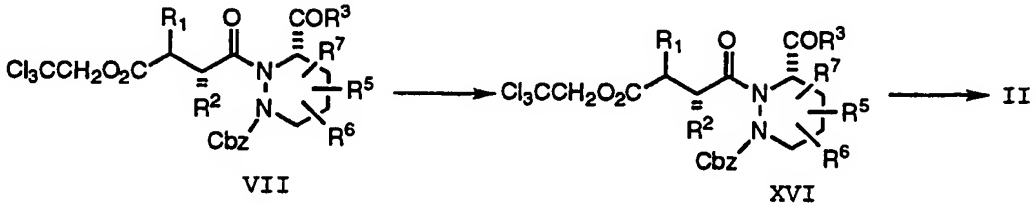
Compounds of Formula II can also be as illustrated in Scheme 7.

Scheme 7

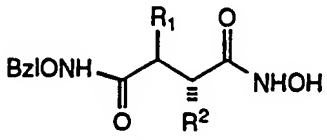


Compounds of Formula II wherein Z is N and R^8 is other than hydrogen are prepared as outlined in Scheme 8. Compounds of Formula (VII) are deprotected as described above followed by alkylation of the resulting free amine with an alkylation agent in the presence of a suitable base. Alkylating agents include alkyl halides, mesylates, tosylates, etc. Suitable bases are triethylamine, N-methylmorpholine or diisopropylethylamine. Compounds wherein R^8 is alkylcarbonyl are prepared by treating deprotected (VII) with an acyl halide such as acetyl chloride.

Scheme 8



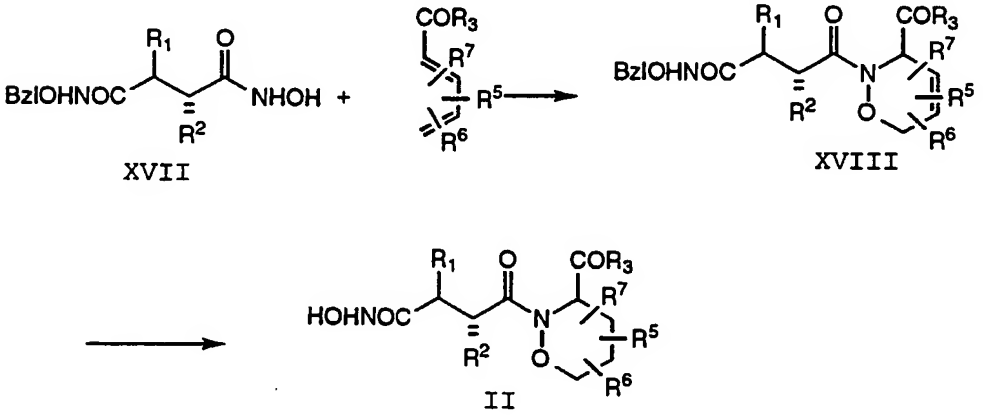
Compounds of formula II wherein Z = O are prepared from hydroxamic acids of formula (XVII) as outlined in Scheme 9.



(XVII)

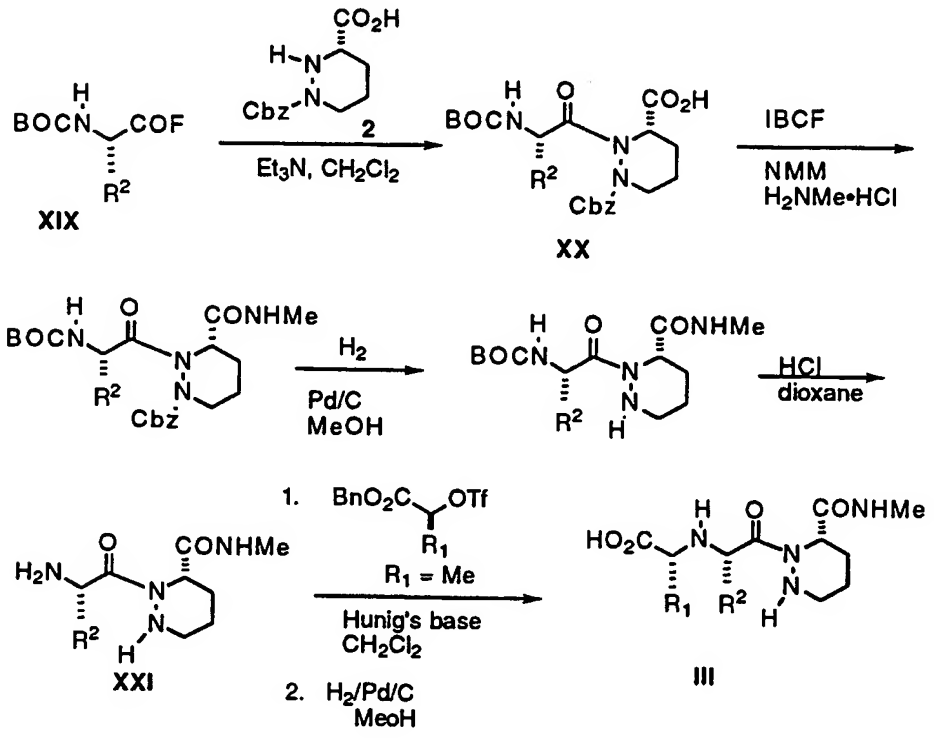
Hetero-Diels-Alder reaction between hydroxamic acids of formula (XVII) and an appropriately substituted diene in the presence of a suitable oxidant gives compounds of formula (XVIII) which upon reduction give compounds of formula II.

Scheme 9



Compounds of Formula I wherein A is -NHCH(R^9)CO_2H are prepared from amino acids (XIX) as by following the steps depicted in Scheme 10.

Scheme 10

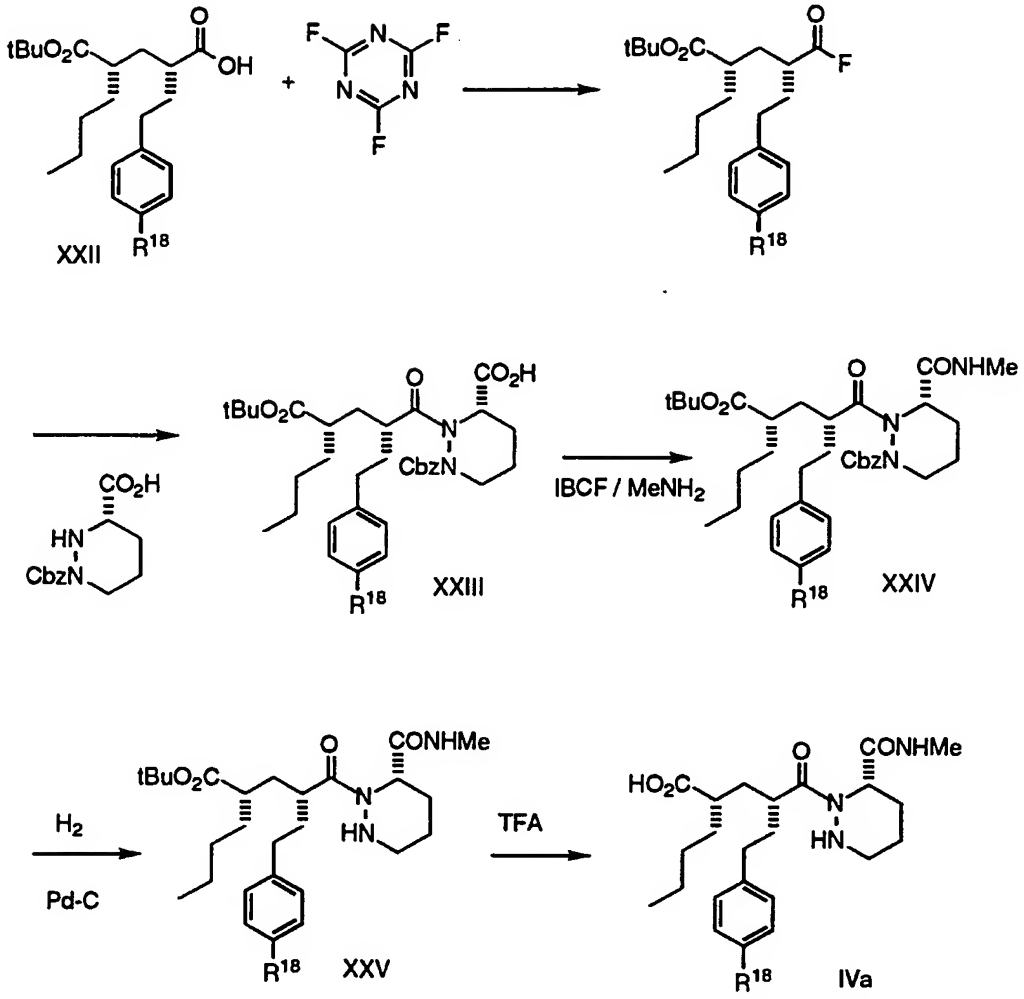


An N-protected amino acid (XIX) fluoride (prepared as described by Carpino et al., J. Org. Chem. 1991 56, 2612) is coupled with piperazic esters of formula (XV) in the presence of an organic amine base such as triethylamine, to give hydrazide (XX). Further elaboration of the t-Butyl ester as described above and hydrogenation of the Cbz-protecting groups followed by hydrolysis of the BOC group gives an amine of formula (XXI). Alkylation of XXI with a suitable halide or triflate in the presence of a base such as Hunig's base, followed by deprotection if necessary, provides compounds of general III. Using methods described above, compound (XV) can be replaced with other N-

heterocycles or aryl or heteroaryl derivatives to give additional compounds of Formula III.

Compounds of Formula I wherein A is $-CH(R^{11})C(R^{9a})(R^{9})CO_2H$ are prepared from acids (XXII) as depicted in Scheme 11 using methods described above. Carboxylic acid (XXII) is converted to the acid fluoride by the method dexcribed by Carpino (vide supra) using cyanuric fluoride. Treatment with Cbz-protected piperazic acid provides the coupled compounds XXIII. The acid is subsequently converted to an amide by activation as described above to give compounds of formula XXIV. Removal of the Cbz protecting group by catalytic hydrogenation followed by deprotection of the t-butyl ester with trifluoroacetic acid provides compounds of formula IVa.

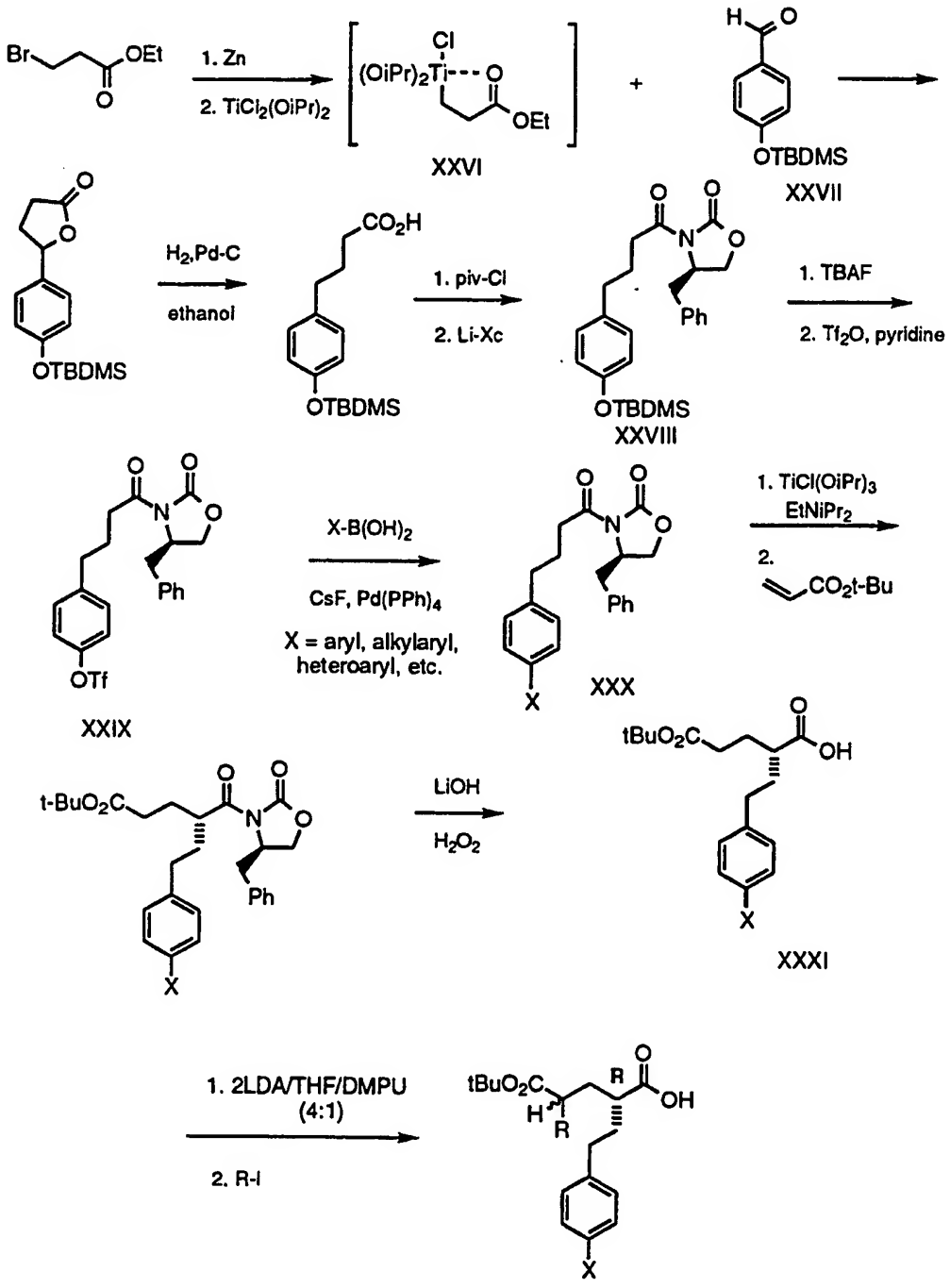
Scheme 11



The acids of formula (XXII) are prepared as illustrated in Scheme 12. Reaction of the titanium homoenolate of ethyl bromopropionate, (XXVI) with a suitably protected 4-hydroxybenzaldehyde, such as (XXVII) provides an intermediate lactone which is reduced by catalytic hydrogenation and converted to the Evans chiral oxazolidinone (XXVII). Removal of the silyl protecting group follwed by conversion to the corresponding triflate using standard conditions (triflic anhydride and pyridine) provides (XXIX). The triflate may then be coupled to aryl boronic acids or

aryl zinc reagents to afford biaryl compounds (XXX). Asymmetric Micahel addition of (XXX) to t-butyl acrylate follwed by removal of the chiral auxiliary with lithium hydroxide/hydrogen peroxide gives (XXXI). Dianion formation with 2 equivalents of lithium diisopropyl amide in tetrahydrofuran/DMPU followed by alkylation with an appropriate alkyl iodide gives XXII, suitably functionalized for coupling as described above.

Scheme 12


1. Zn
2. TiCl2(OiPr)2
XXVI
XXVII
OTBDMS
H2,Pd-C
ethanol
1. piv-Cl
2. Li-Xc
1. TBAF
2. Tf2O, pyridine
XXVIII
X-B(OH)2
CsF, Pd(PPh)4
X = aryl, alkylaryl, heteroaryl, etc.
1. TiCl(OiPr)3
EtNiPr2
2. CO2t-Bu
XXX
XXIX
LiOH
H2O2
XXXI
1. 2LDA/THF/DMPU (4:1)
2. R-I

Unusual amino acids used in this invention can be synthesized by standard methods familiar to those skilled in the art ("The Peptides: Analysis, Sythesis, Biology, Vol. 5, pp. 342-449, Academic Press, New York (1981)). N-Alkyl amino acids can be prepared using procedures described in Cheung et al. (*Can. J. Chem.* **55**, 906 (1977)) and Freidinger et al., (*J. Org. Chem.* **48**, 77 (1982)), which are incorporated herein by reference.

The functional groups of the constituent amino acids must be protected during the coupling reactions to avoid undesired bonds being formed. The protecting groups that can be used are listed in Greene, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Sythesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference.

In a second aspect of this invention, we claim that pharmaceutical preparations of compounds of formula **I** (with the indicated provisos) are orally bioavailable drugs useful for the treatment of arthritis by their action as cartilage protectants.

The compounds of this invention and their preparation can be further understood by the following procedures and examples, which exemplify but do not constitute a limit of their invention.

Examples

Abbreviations used in the Examples are defined as follows: "1X" for once, "2X" for twice, "3X" for thrice, "bs" for broad singlet, "°C" for degrees Celsius, "Cbz" for benzyloxycarbonyl, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H"

for hydrogen or hydrogens, "^{1}H" for proton, "hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "mp" for melting point range, "MHz" for megahertz, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β, "R" and "S" are stereochemical designations familiar to those skilled in the art.

Procedure 1

Preparation of N^1-benzyloxycarbonyl-S-piperazic acid tert-butyl ester

A. [4S-(phenylmethyl)-2-oxazolidinyl)]-5-bromovaleramide

Bromovaleric acid (68g, 0.38 mol) was dissolved in dry methylene chloride (640 ml) and anhydrous DMF (1ml) was added. The solution was cooled to 0° C under an atmosphere of nitrogen. Oxalyl chloride (36.8 ml, 0.413 mol) was added dropwise over 20 min, followed by continued stirring at 0° C for 1h then at room temperature until gas evolution had ceased (6 h). The solvent was then removed *in vacuo* to yield the crude acid chloride.

To a solution of of (+)-(S)-4-benzyloxazolidinone (66.56 g, 0.376 mol) in tetrahydrofuran (900 ml), cooled to -78° C, was added n-butyl lithium (164 ml, 2.29 M in hexanes) over 1h with mechanical stirring. Following an additional stiring period of 15 min, the acid chloride (pre-cooled to -78° C in a jacketed addition funnel) was added over 45 min. The cooling bath was then removed, and the solution allowed to continue stirring over 18 h. The reaction was quenched with 10% citric acid (400 ml) and water (600 ml). The phases were separated, and the aqueous phase was extracted with ether (3 X 300ml). The combined organics were washed with saturated aqueous sodium bicarbonate solution (2 x 600 ml), 10 % citric

acid (2 x 300 ml), water and brine, then dried over anhydrous magnesium sulfate. Filtration and removal of solvent gave the crude product (124.0 g, 97%). Recrystallization from 10:1 heptane ether provided the pure product in 85% yield. mp 57-59° C. MS m/e 340 $(M+H)^+$. $[\alpha]_D$ +81.6.

B. N^1,N^2-[di-tert-butoxycarbonyl]-S-piperazic acid [4S-(phenylmethyl)-2-oxazolidinonamide]

A solution of lithium diisopropyl amide wa first prepared as follows; Diisopopylamine (0.801 mol, 112.3 ml in 250 ml tetrahydrofuran) was cooled to 0° C and treated with n-BuLi (2.5M in hexanes, 0.785 mol, 314 ml) and allowed to stir for 20 min. The solution was then cooled to -78 and the compound of Procedure 1A (250 g, 0.735 mol) in 625 ml THF was added at such a rate as to maintain the internal temperature of the reaction mixture at or below -70° C. Upon completion of the addition, the mixture was allowed to stir an additional 2 h at -78° C. A solution of di-tert-butyl diazodicarboxylate (203 g, 0.882 mol) in dry methylene chloride (370 ml) was then added dropwise at such a rate so as to maintain the internal temperature below -70° C, The resulting mixture was stirred for an additional 15 min, followed by addition of tetrabutyl ammonium iodide (40g, 0.110 mol) and continued stirring at -78° C for 5 min. The reaction temperature was then raised to -20 °C and the mixture was allowed to stir for 18 h whereupon HPLC analysis showed complete conversion to product. The crude mixture was poured into a solution of ether (800 ml), water (2 L) , and potassium dihydrogen phosphate (50 g). The organic layer was separated, and the aqueous further extracted with ether. The combined organics were washed with saturated aqueous sodium hydrogen bicarbonate solution (500 ml) and brine followed by drying over anhydrous magnesium sulfate. Filtration and solvent evaporation gave 443 g of product which was

purified by MPLC-SiO_2 (25% ethyl acetate/hexane)to yield the desired product (417 gm, 91%). MS m/e 507 $(M+H)^+$. $[\alpha]_D$ = +35.95 (c 0.370, methanol). A related procedure for the preparation of this compound is detailed in the literature (Hale et al, Tetrahedron Letters 1992, 33, 7613).

C. S-piperazic acid [4S-(phenylmethyl)-2-oxazolidinonimide] dihydrochloride

To a cooled solution of 4N hydrogen chloride in dioxane (100 ml) was added a solution of the compound of Procedure 1B (10 g, 0.02 mol) in dioxane (10 ml). The cooling bath was then removed, and the solution was allowed to stir for 4 h at room temperature. The solvent was removed *in vacuo* to give the desired dihydrochloride salt (7.3 g, 98%). MS 290 m/e (M+H), $[\alpha]_D$ = +89.29 (c 0.224, methanol), ir 3434, 1782, 1698, ^{1}HNMR(300 MHz) 7.25 (5H, m), 4.81 (1H, dd), 4.40 (1H, m), 4.22 (1H, dd), 3.01 (4H, m), 2.0-1.75 (3H, m), 1.6 (1H, m).

D. N^1-(benzyloxycarbonyl)-S-piperazic acid [4S-(phenylmethyl)-2-oxazolidinonimide]

A solution of the compound of Procedure 1C (8.03 g, 22.1 mmol) in DMF (45 ml) cooled to 0° C was treated with Hunigs base (15.8 ml, 90.4 mmol) and allowed to stir for 20 min. Benzyl chloroformate (3.76 g, 22.1 mmol) was added dropwise over 20 min, followed by removal of the cooling bath and continued stirring at 20° C for 18 h. Evaporation of the volatiles left a brown oil that was taken up in ethyl acetate. The white precipitate (diisopropylethylamine hydrochloride) was removed by filtration, and the filtrate was washed with saturated sodium bicarbonate, water and brine, followed by drying over anhydrous magnesium sulfate. Filtration and solvent removal *in vacuo* gave a semi-solid that was recrystallized from pentane/ethyl acetate to give the

desired product (6.36 g, 68%, 1st crop). mp 102-103° C. MS m/e 423 $(M+H)^+$. $[\alpha]_D$=+33.3 (c 0.664, MeOH).

E. N^1-(benzyloxycarbonyl)-S-piperazic acid

The compound of Procedure 1D (5 g, 11.8 mmol) was dissolved in a mixture of THF (50 ml) and water (10.2 ml) and cooled to 0° C. Lithium hydroxide monohydrate (1.16 g) was added, and the disappearance of starting material was monitored by tlc (1:1 ether/hexane). Upon completion of reaction (approximately 4h), the reaction was quenched with 10% citric acid and extracted with ethyl acetate. The ethyl acetate phase was then extracted 5 times with saturated sodium bicarbonate solution. The aqueous base phase was acidified with citric acid, and extracted 4 times with ethyl acetate. The organic phase was then washed with water, brine and dried over anhydrous magnesium sulfate. Solvent evaporation gave the desired product (2.9 g, 93%) which was used without purification in the next step. MS m/e 282 $(M+H)^+$, $[\alpha]_D$ = -31.25 (c 0.0128, MeOH), ir 3200, br, 1750, 1692 ^{1}HNMR(300 MHz) 7.28 (5H, m), 5.05 (2H, s), 3.8 (1H, ddd), 3.28 (2H, m), 3.02 (1H, m), 1.85 (1H, m), 1.70 (1H, m), 1.5 (2H, m).

F. N^1-(benzyloxycarbonyl)-S-piperazic acid tert-butyl ester

To a solution of the the compound of Procedure 1E (11 g) in methylene chloride (100 ml), was added N,N-diisopropyl-O-tert-butyl imidate•$CuCl_2$ (35 ml of a 3 M solution in methylene chloride), and the whole was allowed to stir at 20° C for 18 h. Acetic acid (20 ml) was added, and the solution was stirred for an additional 30 min. Filtration, followed by dilution with water (100 ml) and saturated sodium bicarbonate solution until basic (pH 9-10) gave a solution that was stirred vigorously for another 10 min. Separation of the organic phase followed by extraction with methylene chloride

gave the product layer which required an additional filtration to remove a blue gelatinous precipitate. The aqueous layer was extracted an additional 3 times with methylene chloride, and the combined organics were washed with water, brine and then dried over anhydrous magnesium sulfate. Solvent removal *in vacuo* gave an oil that was triturated with hexane and filtered to remove any residual solid. Removal of the hexane gave the desired product as an oil (10.3 g, 88%) that solidified on standing at -20° C. MS m/e 280 $(M+H)^+$, $[\alpha]_D$ = -33 (c 0.700, MeOH), ir 1732, 1698.

Procedure 2

Preparation of N^1-(benzyloxycarbonyl)-6-phenylpiperazic acid tert-butyl ester

A. 2-Carbomethoxy-5,8-diphenylbicyclo [4.3]-1,6,8-triaza-7,9-dioxonon-3-ene

To a suspension of N-phenyl-3,4-dioxourazole (9.55 g 54.5 mmol) in methylene chloride (250 ml) was added a solution of methyl 5-phenyl-2,4-pentenoate (10.25g, 54.5 mmol) in methylene chloride (100 ml) over 20 minutes. The mixture was allowed to continue stirring at room temperature for 18h. The solvent was removed by on a rotary evaporator to give a semi-solid that was triturated with 1:1 ether/hexane. The white crystals were collected by filtration to give the product (12.34 g, 65%). The trituation was repeated on the filtrate to give an additional crop of white cyrstalline product, for a combined yield of 14.16 g (75%). mp. 155-156° C. MS m/e 364 $(M+H)^+$.

B. 2-Carbomethoxy-5, 8-diphenylbicyclo [4.3]-1,6,8-triaza-7,9-dioxononane.

The product of Procedure 2A (14.16g, 39.9 mmol) was diluted with a 3:1 mixture of ethanol/ethyl acetate, and

stirred in the presence of 10% palladium on carbon under 1 atm of hydrogen pressure for 18 h. The catalyst was removed by filtration and washed with methylene chloride. Solvent was removed by evaporation to give a white solid foam (14.2 g, 100%). Trituration of the foam with 1:1:1 Ethyl acetate/ether/hexane, filtration and drying gave the desired product (12.7g, 90%). mp 126-128° C. MS 366 $(M+H)^+$.

C. 6-Phenylpiperazic acid dihydrochloride

The compound of Procedure 2B (28.7 g, 78.6 mmol), butanol (210ml) and powdered potassium hydroxide (28.7g, 511 mmol) were combined and heated to reflux for 24h. The mixture was cooled to room temperature and allowed to stir for an additional 24h. Water (225 ml) was added, and the mixture stirred for 30 min. The butanol layer was separated and washed with water (225 ml). The combined aqueous phases were washed once with methylene chloride. The aqueous phase was then acidified to pH 2 using 6N HCl. Evaporation of the volatiles under high vacuum gave a solid that was triturated with methanol. The potassium chloride was filtered off and the solvent was removed to yield the desired product (21.5 g, 96%). MS m/e 207 $(M+H)^+$ of free base.

D. N^1-(Benzyloxycarbonyl) piperazic acid

The compound of Procedure 2C (1g, 3.6 mmol) was dissolved in water (15 ml) and adjusted to pH 9-9.5 with 2N sodium hydroxide. The resulting mixture was then cooled to 5° C, and a solution of benzylchloroformate (0.464 ml, 3.6 mmol) in toluene (2ml) and a solution of sodium hydroxide (3.58 mmol) in water (2ml) were added simultaneously and at equal rates over 5 min. The biphasic solution was allowed to stir for 18h. The solution was then acidified to pH 3 using 1N HCl, and the mixture extracted with ethyl acetate (3X). The organic phase was washed with brine and dried over

anhydrous magnesium sulfate. Filtration, followed by solvent evaporation *in vacuo* gave the title compound (1.16g, 95%). This material was used crude in the next step. MS m/e 341 $(M+H)^+$, 295 (M^+-CO_2), 251 $(M^+$-benzyl).

E. N^1-(benyloxycarbonyl)-6-phenylpiperazic acid t-butyl ester.

A solution of the compound of Procedure 2D (1.22g, 3.6 mmol) in methylene chloride (10 ml), cooled to 0°C, was treated with N,N-disopropyl- O-tert-butylimidate•$CuCl_2$ (3.5 ml, 3.5M solution). The cooling bath was removed, and the solution was allowed to stir for 4.5 h at room temperature. The material was worked up as described previously in the procedure of Procedure 1F. The crude material (1.24g, 86%) was purified by MPLC (SiO_2, 4:1 hexane/ethyl acetate) to give the product as a mixture of diastereomers. MS 397 $(M+H)^+$.

Procedure 3

Preparation of (2S,3R)-2'2'2'-Trichloroethyl 3-carboxy-2,5-dimethylhexanoate

A. (R)-2-Ethenyl-3-(t-butoxycarbonyl)-5-methylhexanoic acid

(R)-Benzyl (2-benzyloxycarbonyl)-3-(tert-butoxycarbonyl)-5-methylhexanoate (2 g, 4.4 mmol) was prepared as described in European Patent Application WO 90/05719) and dissolved in ethanol (40 ml). Ammonium formate (1.4 g, 21.3 mmol) was added followed by 10% Pd-C (500 mg) as an isopropanol slurry. After 90 min, the catalyst was removed by filtration through celite to give a solution of the crude diacid. Piperidine (415 g) was added and the mixture was allowed to stir for 10 min at room temperature. Aqueous formaldehyde (2.1 ml, 40% solution) was added, and the mixture was allowed to stir for an additional 18 h. The solution was then heated to reflux for 90 min, cooled to room temperature, and the solvent evaporated. The crude material was partitioned

between ethyl acetate and 10% citric acid solution. The acid layer was extracted with ethyl acetate 3X, and the combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. to yield of the title compound (0.87 g, 82%) as a colorless oil. MS m/e 242 $(M+H)^+$; IR 3500-2800, 1730, 1700, 1626 cm^{-1}.

B. 2S-Methyl-3R-(tert-butoxycarbonyl)-5-methylhexanoic acid

To a solution of the compound of Procedure 3A (0.86 g) in methanol (40 ml) was added 10% Pd-C (120 mg), and the heterogeneous mixture was stirred under 1 atm hydrogen gas for 12 h. The catalyst was filtered, and the solvent evaporated to give the saturated product as a colorless oil (9:1 mixture of diastereomers). MS m/e 244 $(M+H)^+$, [α] +18.2 (c 0.406, methanol)

C. 2'2'2'-Trichloroethyl 2S-methyl-3R-(tert-butoxycarbonyl),5-methylhexanoate

The compound of Procedure 3B (4.4 mmol), trichloroethanol (850 ml, 8.8 mmol), and DMAP (30 mg) were combined in dry methylene chloride (10 ml) and cooled to 0° C. Dicyclohexylcarbodiimide (908 mg (4.4 mmol) was added, the cooling bath removed after 5 min and the solution allowed to stir under a nitrogen atmosphere for 12 h. The dicyclohexylurea precipitate was removed by filtration, followed by washing the organic layer with 10% citric acid and brine. Evaporation of the solvent gave a semi-solid which was triturated with hexane to give another crop of the urea that was also collected by filtration. The hexane layer was stirred vigorously over an equal volume of water for 2 h to remove excess trichloroethanol. The hexane layer was then separated, washed with brine and dried over $MgSO_4$. Evaporation of solvent gave a crude oil that was purified by silica gel MPLC (5% ether/hexane) to give

the desired pure diastereomer as an oil (77 %). MS m/e 376 $(M+H)^+$, $[\alpha]_D$ = +7.43 (c 0.350, methanol).

D. (2S, 3R)-2'2'2'-Trichloroethyl 3-carboxy-2,5-dimethylhexanoate

The product of Procedure 3C (5 g, 3.3 mmol) was added to a 4N soultion of HCl in dioxane (125 ml) and stirred at room temperature for 8 h. The solvent was then removed in vacuo to give the title acid (4.2 g, 98%). MS m/e 319 $(M+H)^+$, $[\alpha]_D$ = +9.8 (c 9.8, methanol).

Example 1

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide

A. (2R,3S)-[4-(2'2'2'-trichloroethoxy)-2-isobutyl-3-methylsuccinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid tert-butyl ester

The compound of Procedure 3D (1 g, 3.1 mmol) was dissolved in dry methylene chloride (30 ml), containing 5 drops of dry N,N-dimethylformamide. The solution was cooled to 0° C under N_2 followed by addition of oxalyl chloride (0.297 ml, 3.4 mmol). The solution was allowed to stir 30 min at 0° C and then 1 h at RT. The solvent was evaporated in vacuo 3X with washing with dry methylene chloride to remove HCl. The crude acid chloride was dissolved in 15 ml methylene chloride and added to a mixture of the (+/-)-t-butylester of N^1-benzyloxycarbonylpiperazic acid (992 mg, 3.1 mmol) and N-methylmorpholine (341 ul, 3.1 mmol) in methylene chloride (20 ml) at 0° C. The mixture was then allowed to stir for 18 h at room temperature, then diluted with 10% citric acid, followed by separation and washing with saturated aqueous sodium bicarbonate, brine and then dried over anhydrous magnesium sulfate. The solvent was evaporated to give crude material that was purified by silica gel MPLC to give the title compound (0.96 g, 50%)

as a 1:1 mixture of diastereomers. MS m/e 623 $(M+H)^+$. IR 1760 cm^{-1}.

B. (2R,3S)-[4-(2'2'2'-trichloroethoxy)-2-isobutyl-3-methylsuccinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

The compound of example 1A (0.96 g) was added to a solution of 4N HCl/dioxane (35 ml) and allowed to stir for 8 h at room temperature. Solvent removal *in vacuo* gave the desired acid in quantitative yield. The crude acid was dissolved in methylene chloride (10 ml) was treated with N-methylmorpholine (0.19 ml, 1.7 mmol) and cooled to -20° C. After stirring for 10 min at -20, isobutylchloroformate (0.2 ml, 1.5 mmol) was added dropwise over 5 min, and the solution was allowed to stir for 1 h at that temperature. The resulting mixture was treated with 5 equivalents of 40% aqueous methylamine, and the solution was allowed to stir for 30 min over which time ambient temperature was reached. The mixture was then diluted with ethyl acetate, washed with 10% citric acid, water and brine then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude oil that was purified by MPLC (5% MeOH/methylene chloride) to give the desired amide as a 1:1 mixture of diastereomers (770 mg, 89%). MS m/e 578 $(M+H)^+$, IR 3354, 1752, 1716, 1678, 1544 cm^{-1}.

C. (2R,3S)-[4-hydroxy-2-isobutyl-3-methylsuccinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

The compound of Example 1B was dissolved in tetrahydrofuran (26 ml) to which was added 5.2 ml of a 1 M solution of ammonium acetate. The solution was cooled to 0° C and Zn powder (2.3 g, 3 wt. equivs.) was added. The heterogeneous solution was vigorously stirred for 10 min at 0° C and an additional 6 h at room temperature. The crude reaction mixture was filtered and washed with ethyl acetate. The solvent was then removed by

evaporation, and the crude material was taken up in ethyl acetate and washed with water, 10% citric acid (2x), brine and then dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent, followed by MPLC (10% MeOH/methylene chloride) gave the desired product in a 1:1 mixture of diastereomers as a white foam (330 mg, 57%). MS m/e 465 $(M+H)^+$, IR 3324, 2958, 1712, 1680, 1554 cm^{-1}.

D. (2R,3S)-[4-(benzyloxyamino)-2-isobutyl-3-methylsuccinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

The compound of Example 1C (210 mg, 0.47 mmol) was combined with N-methylmorpholine (0.056 ml) in dry methylene chloride (15 ml) and cooled to -20° C under N_2. Isobutylchloroformate (0.061 ml, 0.47 mmol) was added, and the solution was allowed to stir for 1h. A solution of O-benzylhydroxylamine hydrochloride (77 mg) and N-methylmorpholine (0.056 ml) in methylene chloride (3 ml) was added with washing with methylene chloride, and the mixture was allowed to stir at room temperature for 18 h. The mixture was then diluted with methylene chloride, washed with 10% citric acid (1x20 ml), brine and then dried over anhydrous magnesium sulfate. Evaporation of solvent gave of the O-benzyl protected hydroxamic acid (203 mg, 78%) as a mixture of diastereomers which were separated by HPLC C_{18} column, 10% isopropanol/hexane.

Diastereomer A 97 mg (first product to elute)was converted to the corresponding hydroxamic acid as detailed in Example 1E below.

Diastereomer B 95 mg (second product to elute) was converted to the corresponding hydroxamic acid as detailed in Example 2 below.

E. (R)-[(2R,3S)-4-(N-hydroxyamino)-2-isobutyl-3-methylsuccinyl]-N^2-piperazic acid-N-methyl amide

Diastereomer A of Example 1D (29 mg, 0.052 mmol) was dissolved in ethanol (5 ml) and 10% Pd on C (5 mg) was added. The solution was stirred under a balloon of hydrogen for 1h. The heterogeneous mixture was filtered through a microporous filter, and evaporated to dryness to give the title compound (18 mg, quantitative yield). MS m/e 570 $(M+H)^+$, $[\alpha]_D$ +54.17 (c 0.216, MeOH), mp 120-130 °C, ir 3224, 1624 br, 1HNMR (400 MHz, COSY, CD_3OD) 5.1 (1H, dd), 4.08 (1H, dt), 3.09 (1H, ddd), 2.79 (3H, s) 2.4 (1H, ddd), 2.25 (1H, ddd), 2.19 (1H, dddd), 1.8 (1H, dddd), 1.65 (1H, ddd), 1.55 (2H, m), 1.4 (1H, m), 1.2 (3H, d), 1.19 (1H, m), 0.92 (3H, d), 0.88 (3H,d), ^{13}CNMR (100 MHz, DEPT, CD_3OD) 178.7, 174.8, 173.6, 42.9, 41.7, 41.0, 27.5, 27.3, 26.3, 24.2, 22.3, 22.2, 15.5.

Example 2

(S)-[(2R,3S)-4-(N-hydroxyamino)-2-isobutyl-3-methylsuccinyl]-N^2-piperazic acid-N-methyl amide

Diastereomer B of Example 1D (15 mg) was dissolved in ethanol (5 ml) and 10% Pd on C (5 mg) was added. The solution was stirred under a balloon of hydrogen for 1h. The heterogeneous mixture was filtered through a microporous filter, and evaporated to dryness to give the title compound (10 mg,). mp 123-127 °C, MS m/e 570 (M+H)+, $[\alpha]_D$ +6.67 (c 0.009, MeOH), ^{1}HNMR (400 MHz, COSY, CD_3OD) 5.15 (1H, dd), 4.0 (1H, m), 3.05 (1H, m), 2.8 (1H, m), 2.79 (1H, s), 2.28 (1H, m), 2.10 (1H, m), 1.9 (1H, m), 1.7-1.5 (3H, m), 1.3 (1H, m), 1.05 (1H, m), 1.04 (3H, d), 0.92 (3H, d), 0.83 (3H, d), 13CNMR (100 MHz, DEPT, CD_3OD) 180.8, 179.11, 174.6, 52.4, 42.6, 42.5, 28.1, 27.5, 27.1, 227.0, 26.2, 24.5, 22.4, 17.3, 17.1.

Example 3

N-[1(R)-carboxyethyl]-α-(S)-isobutylglycine-(S)-N^1-piperazic acid methyl amide

To a solution of Cbz-L-Leucine (1g, 3.77 mmol) and N,N-dimethylformamide (0.5 ml) in methylene chloride (45 ml) at 0°, was added oxalyl chloride (0.329 ml). The

solution was stirred for 1 h at 0° and then 2h at room temperature. The solution was then evaporated *in vacuo*. The crude acid chloride was then taken up in methylene chloride (45 ml) and cooled to 0° under N_2. The compound of Procedure 1F (1.21 mg, 3.77 mmol) and N-methylmorpholine (0.458 ml) in methylene chloride was added to the solution of acid chloride over 10 min , and the whole was allowed to stir for 18h at RT. The mixture was taken up in methylene chloride and washed with 10% citric acid, saturated aqueous sodium bicarbonate, water, brine and then dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent gave the amide as an oil that was purified by MPLC (1.7 g, 79 %)

This amide (1.7 mg,2.98 mmol) was treated with trifluoroacetic acid for 4 h at room temperature. Solvent evaporation gave the intermediate acid which was used without further purification in the next step. To a -20° C solution of the crude acid (660 mg, 1.29 mmol) and N-methylmorpholine (0.145 ml, 1.37 mmol) in methylene chloride was added isobutylchloroformate (0.173 ml, 1.32 mmol). The solution was allowed to stir for 1 h at -20. Aqueous methylamine (40% solution, 5 equiv) was added and the temperature allowed to increase to ambient. After 1h, the solution was quenched with 10% citric acid, diluted with methylene chloride and washed with water and brine folloed by drying over MgSO4. Filtration and solvent evaporation gave the methyl amide which was purified by MPLC.

The bis-Cbz protected intermediate was hydrogenated with H_2 Pd-C in ethanol for 4 h at 1 atm. The heterogeneous mixture was filtered and evaporated in vacuo to give the corresponding amine. The final product was obtained by performing a reductive amination with benzyl pyruvate as described in the following: The amine in THF was treated with benzyl pyruvate at 20 °C. Sodium cyanoborhydride was added and an equivalent of p-toluenesulfonic acid in THF was titrated in over 1h. The

solvent was evaporated to approximately 1/3 volume and ethyl acetate and water were added. The organic phase was separated and the aqueous washed an additional 3 times with ethyl acetate. The combined organics were washed with water and brine then dried over MgSO4. Filtration and solvent evaporation gave the crude amino acid as a mixture of diastereomers which was purified by MPLC (60% MeOH/methylene chloride). MS m/e 327 $(M+H)^+$

Example 45a

(S)-[(2R)-4-(N-hydroxyamino)-2-propylphenyl-succinyl]-N^2-piperazic acid-N-methyl amide

A. [4S-(phenylmethyl)-2-oxazolidinyl)]-5-phenylvaleramide

The sodium salt of 5-phenylvaleric acid (53.5 mol) was dissolved in dry THF (100 ml) and anhydrous DMF (1ml) was added. The solution was cooled to 0° C under an atmosphere of nitrogen. Oxalyl chloride (4.67 ml) was added dropwise over 20 min, followed by continued stirring at 0° C for 1h then at room temperature until gas evolution had ceased (3 h).

To a solution of of (+)-(S)-4-(phenylmethyl)-oxazolidinone (8.83 g, 53.5 mmol) in tetrahydrofuran (100 ml), cooled to -78° C, was added n-butyl lithium (21.4 ml, 2.5 M in hexanes) over 1h with stirring. Following an additional stiring period of 15 min, the acid chloride (pre-cooled to -78° C in a jacketed addition funnel) was added over 45 min. The cooling bath was then removed, and the solution allowed to continue stirring over 18 h. The reaction was quenched with 10% citric acid (100 ml) and water (100 ml). The phases were separated, and the aqueous phase was extracted with ether (3 X 300ml). The combined organics were washed with saturated aqueous sodium bicarbonate solution (2 x 600 ml), 10 % citric acid (2 x 300 ml), water and brine, then dried over anhydrous magnesium sulfate. Filtration

and removal of solvent gave the crude product which was chromatographed using 20% ethyl acetate/hexane to give 14 g (77%) of the desired product. MS m/e 338 (M+H).

B. [4S-(phenylmethyl)-2-oxazolidinyl)]-2S-(t-butylacetyl)-5-phenylvaleramide.

The compound of Part A (14 g, 41.5 mmol) was dissolved in 150 ml anhydrous THF and cooled to -78 under N_2. LDA (41.5 mmol) was added over 10 min., and the solution was stirred at -78 for 30 additional minutes. Tert-butyl bromoacetate (8.1 g, 41.5 mmol) dissolved in 30 ml THF was added over 20 min, and the resulting mixture was allowed to stir at -78 for 30 min then warmed to ambient temperature by removal of the cooling bath. After 1 h, the solution was concentrated on a rotary evaporator to 1/4 volume. Ethyl acetate was added followed by washing with 10% citric acid, water then brine and dried over MgSO4. Solvent evaporation gave an oil that was purified by MPLC 25% ether/hexane to give 10.75 g (57%) of the addition product. mp 73-75 °C, MS m/e 452 $(M+H)^+$, $[\alpha]_D$=+74.3 (c 0.214, methanol).

C. Tert-Butyl-3R-(hydroxycarbonyl)-6-phenylhexanoate

To a cooled solution (0 °C)of the compound of Part B (5 g, 11.1 mmol) dissolved in 60 ml of THF/H_2O (4:1) was added hydrogen peroxide (30% solution, 4.5 ml, 44.4 mmol) was followed by aqueous LiOH (425 mg in 30 ml water). The solution was allowed to stir for 5 h at 0, at which time complete consumption of starting material was observed by tlc. The THF was removed under reduced pressure, and the resulting aqueous phase washed with methylene chloride. The water phase was then carefully acidified to pH 1 with 10% HCl. The solution was then extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated to give the crude product. The material was purified by MPLC 7% methanol/methylene chloride to provide 2.90 g (90%) of purified acid. MS m/e 293 $(M+H)^+$, $[\alpha]_D$=+6.3 (c 0.322, methanol).

D. (2R)-[4-(tert-butoxy)-2-(3-phenylpropyl)succinyl]-N^2-(N^1-benzyloxycarbonyl)-S-piperazic acid

The compound of Part C (2.50 g, 8.56 mmol) was dissolved in 100 ml of anhydrous toluene and cooled to -10 °C. DMF (0.5 ml) was added followed by oxalyl chloride (1.39 g). The resulting solution was allowed to stir for 1h at -10, followed by evaporation of solvent under high vac at -10. Th crude acid chloride was then diluted with 50 ml methylene chloride, and cooled to 0o under N2. In a separate flask, N-benzyloxycarbonyl-S-piperazic acid (2.26g) was dissolved in 35 ml methylene chloride and treated with 3.68 ml of triethylamine. After 5 min, this solution was transferred to a dropping funnel and added to the aboveover 10 min. Stirring was continued for 1 h at 0 and 1 h at ambient temperature. The reaction was then quenched with 10% citric acid and extracted 3 times with methylene chloride. The organic phase was then washed with water, brine, then dried over $MgSO_4$. Filtration and solvent evaporation followed by MPLC (7% MeOH / methylene chloride) gave 1.95 g (42%) of the desired product. MS m/e 539 $(M+H)^+$, $[\alpha]_D$=-10.6 (c 1.002, methanol).

E. (2R)-[4-(tert-butoxy)-2-(3-phenylpropyl)succinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

To the compound of Part D (1.90 g, 3.53 mmol) dissolved in 40 ml methylene chloride, was added, NMM (413 ul). The solution was cooled to -20, followed by addition of IBCF (459 ul, 3.53 mmol). The mixture was allowed to stir for 1.5 h followed by the addition of 0.6 ml of 40% aqueous methyl amine. The cooling bath was removed and the solution was allowed to stir for 1 h at ambient temperature. The reaction was quenched by the addition of 10% citric acid. The organic phase was separated, washed with water, brine and then dried over $MgSO_4$. Filtration and solvent evaporation gave the crude

product which was purified by MPLC (75% MeOH / methylene chloride) to give 1.6 g (82%) of product. MS m/e 552 $(M+H)^+$, $[\alpha]_D$=-29.9 (c 0.166, methanol).

F. (2R)-[4-hydroxy-2-(3-phenylpropyl)succinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

1.6 g of the compound of Part E was treated with 50 ml of 4N HCl in dioxane for 2h. The solvent was then evaporated under reduced pressure to give the crude acid, which was purified by MPLC (7% MeOH / methylene chloride ramped to 13% MeOH / methylene chloride). 930 mg (65%) of pure desired product was obtained. MS m/e 496 $(M+H)^+$, $[\alpha]_D$=-34.8 (c 0.118, methanol)

G. (2R)-[4-(benzyloxyamino)-2-(3-phenylpropyl)succinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

In a manner analogous to example 1D the title compound was prepared from 930 mg of compound of Example 45a, Part F to give 620 mg (54%) of the desired product. MS m/e 601 $(M-CH_3)^+$, $[\alpha]_D$=-30.7 (c 0.114, methanol).

H. (2R)-[4-(hydroxyamino)-2-(3-phenylpropyl)succinyl]-N^2-(N^1-benzyloxycarbonyl)-piperazic acid N-methyl amide

In a manner analogous to 1E, the title compound was obtained in 80% yield (40 mg). MS m/e 376 (M+H)+, $[\alpha]_D$= -12.5 (c0.080, methanol), 1HNMR (MeOH - d4) 7.25-7.15 (5H,m), 5.05 (1H, m), 3.9 (1H, m), 2.95 (1H,m), 2.8 (1H,m), 2.76 (3H,s), 2.6 (2H,m), 2.5 (1H, dd), 2.19 (1H, dd), 2.01 (1H,m), 1.95 (1H,m), 1.7-1.4 (6H,m)

Example 205

S-[2S-((1R-Carboxy)ethylamino)-4-phenyl)butanoyl]-N^2-piperazic acid, N-methyl amide

A. S-[2S-(t-butyloxycarbonylamino)-4-phenylbutanoyl]-[N^1-benzyloxycarbonyl]-N^2-piperazic acid, mono methylamide

The piperazic acid of Procedure 1, part E (4.35 g, 16.5 mmol) was dissolved in methylene chloride prior to the addition of Hunig's base (5.7 ml, 33.1 mmol). This mixture was cooled to 0°C, and the acid fluoride 1 (4.6 g, 16.5 mmol) in methylene chloride at 0°C was added dropwise. The reaction was warmed to room temperature and was stirred overnight. The reaction was quenched and washed with 10% aqueous citric acid solution. The organic layer was dried, filtered, and concentrated to give the crude acyl hydrazide (8.5 g), which was carried forward. The acyl hydrazide (8.5 g) was dissolved in methylene chloride. At 0°C, N-methylmorpholine (2.5 ml, 19.9 mmol) was added followed by isobutylchloroformate (2.5 ml, 19.2 mmol). After this mixture was stirred at 0°C for 30 min, 40% aqueous methylamine (6.2 g) was added. The mixture was warmed to room temperature and was stirred overnight. The reaction was quenched and washed with saturated $NaHCO_3$ solution. The aqueous layer was dried, filtered, and concentrated. Flash chromatography of the resulting oil gave the desired amide (3.0 g, 5.5 mmol, 33%) as a white foam: MS-CI (m/z) 539 (M^+ + 1, 49%).

B. S-[2S-(t-butyloxycarbonylamino)-4-phenylbutanoyl]-N^2-piperazic acid, mono methylamide

The amide of Ex. 205, Part A (3.0 g, 5.5 mmol) was dissolved in methanol prior to the addition of 10% Pd/C (310 mg). The mixture was stirred under a hydrogen atmostphere for 3 hrs. The Pd/C was removed by filtration, and the resulting solution was concentrated. Flash chromatography provided the desired product (1.86 g, 4.6 mmol, 80%) as a white foam: MS-CI (m/z) 405 (M^+ + 1, 100%).

C. S-[2S-((1R-benzyloxycarbonyl)ethylamino)-4-phenyl)butanoyl]-N^2-piperazic acid, N-methyl amide

The compound of Ex. 205, Part B (1.3 g, 3.2 mmol) was dissolved in 4M HCl/dioxane (60 ml) and was stirred overnight. The solution was concentrated to a white solid before saturated Na_2CO_3 was added. This was extracted with methylene chloride. The organic layer was dried, filtered, and concentrated. This yielded the crude primary amine which was used directly in the next step. Thus, a portion of this primary amine 6 (474.5 mg, 1.56 mmol) was dissolved in methylene chloride and cooled to 0°C prior to the addition of Hunig's base (0.35 ml, 2.0 mmol). This mixture was added to the triflate of benzyl lactate 7 [produced *in situ* from benzyl lactate (365.2 mg), 2,6-lutidine (0.3 ml), and Tf_2O (0.4 ml)] in methylene chloride at 0°C. The reaction was warmed to room temperature and was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and was extracted with methylene chloride. The organic layer was dried, filtered, and concentrated. Flash chromatography provided the desired alkylated amine 8 (87.6 mg, 0.2 mmol, 12%) as a white foam: MS-CI (m/z) 467 (M^+ + 1, 100%).

D. S-[2S-((1R-Carboxy)ethylamino)-4-phenyl)butanoyl]-N^2-piperazic acid, N-methyl amide

The compound of Ex. 205, Part C (72 mg, 0.15 mmol) was dissolved in methanol prior to the addition of 10% Pd/C (10 mg). The mixture was stirred under a hydrogen atmostphere overnight. The Pd/C was removed by filtration, and the resulting solution was concentrated. Trituration with ether provided 10 (56 mg, 0.15 mmol, 99%) as a white solid: mp 118-120°C; MS-CI (m/z) 377 (M^+ + 1, 100%); ^1H NMR (DMSO, 300 MHz, d ppm) 8.02 (m, 1H), 7.3-7.15 (m, 5H), 4.92 (m, 2H), 4.18 (t, 1H), 3.12 (m, 1H), 2.95 (br d, 1H), 2.75-2.5 (m, 5H), 2.04 (br d, 1H), 1.85-1.6 (m, 3H), 1.45 (m, 2H), and 1.19 (d, 3H).

Using the procedure of Ex. 205, the following compounds were similarly prepared.

Example 215

S-[2S-((1R-Carboxy-2-phenyl)ethylamino)-4-phenyl)butanoyl]-N^2-piperazic acid, N-methyl amide

mp 209-211°C; MS-CI (m/z) 453 (M^+ + 1, 100%); ^{1}H NMR (DMSO, 300 MHz, d ppm) 7.98 (m, 1H), 7.3-7.02 (m, 10H), 4.9 (br d, 1H), 4.8 (br d, 1H), 3.88 (m, 1H), 3.23 (m, 1H), 2.88-2.7 (m, 3H), 2.6 (d, 3H), 2.5 (m, 1H), 2.4 (m,1H), 1.99 (br d, 1H), 1.82-1.6 (m, 2H), and 1.57-1.35 (m, 3H).

Example 216

S-[2S-((1R-Carboxy-3-methyl)butylamino)-4-phenyl)butanoyl]-N^2-piperazic acid, N-methyl amide

mp 96-99°C; MS-CI (m/z) 419 (M^+ + 1, 100%); ^{1}H NMR (CD_3OD, 300 MHz, d ppm) 7.3-7.15 (m, 5H), 5.06 (m, 1H), 4.85 (t, 1H), 3.55 (t, 1H), 3.0 (br d, 1H), 2.85-2.7 (m, 6H), 2.3-1.76 (m, 6H), 1.6 (m, 3H), and 0.98 (dd, 6H).

Example 217

S-[2S-((1R-Carboxy-2-phenyl)ethylamino)-4-methyl)pentanoyl]-N^2-piperazic acid, N-methyl amide

mp 179-180°C; MS-CI (m/z) 329 (M^+ + 1, 100%); ^{1}H NMR (CD_3OD, 300 MHz, d ppm) 5.03 (m, 1H), 4.8 (m, 1H), 3.54 (q, 1H), 3.03 (br 1, 1H), 2.85 (td, 1H), 2.75 (s, 3H), 2.13-1.95 (m, 2H), 1.82-1.52 (m,5H), 1.8 (d, 3H), and 0.98 (app t, 6H).

Example 402

2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine

A. 4-[(1,1'-biphenyl)yl]tetrahydrofuran-2-one

To a stirred solution of ethyl 3-iodopropanoate (2.12 g, 9.32 mmol) in anhydrous toluene (15 ml) and freshly distilled N,N-dimethyl acetamide (1.58 ml), was added Zn-Cu complex (0.98 g). The mixture was heated to 80° C for 4h.

To a separate flask containing $Ti(OiPr)_4$ (2.06 ml) in methylene chloride (2 ml), was added dropwise $TiCl_4$ (2.33 ml, 1M soln). The mixture was stirred 15 min then cooled to -40°C. The ZnCu complex above was cooled to room temperature and cannulated into the $TiCl_2(OiPr)_2$ solution and the mixture allowed to stir at -20°C for 20 min and then recooled to -40°C. To this was added 4-phenylbenzaldehyde (1.36 g, 7.46 mmol) in methylene chloride (10 ml) dropwise , and the whole was stirred for 15 min at -40°C then allowed to reach room temperature over 18h. The mixture was then poured into a mixture of 10% HCl and ether and stirred for 10 min. The solution was extracted with ethyl acetate, washed with water, brine, then dried over $MgSO_4$. Following filtration, the crude material was recrystallized from ethyl acetate/hexane to afford the desired pure product (1.42 g, 80%). MP 103.5-104°C; EIMS (M+H) 239; IR (KBr) 1766 cm^{-1}.

B. 4-(1,1'-biphenyl)ylbutanoic acid

To a solution of the compound of Ex. 328, Part A (1.06 g, 4.5 mmol) in methanol (20 ml) and ethyl acetate (10 ml), was added 10% Pd-C (0.10 g). The mixture was treated with H_2 at 1 atm for 1.5 h. The catalyst was removed by filtration and the filtrate evaporated to give the title acid (1.0 g, 94%). MP 119.5-120.5° C; CIMS ($M+NH_4^+$) 258; IR (KBr) 1696, 3026 cm^{-1}.

C. 3-[4-(1,1'-biphenyl)yl-1-oxobutyl]-4(S)-(phenylmethyl)oxazolidin-2-one

The title compound was obtained as an oil in 74% yield using the method described above in Procedure 1, Part A IR (kBr) 3026, 1766, 1696 cm^{-1}; $[\alpha]_D$ = +80.3 (c. 0.36, methanol); HRMS calculated 400.191229, found 400.191814.

D. 3-[4(S)-t-butoxycarbonyl-2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-1-oxobutyl]-4(S)-(phenylmethyl)oxazolidin-2-one

To a stirred solution of $TiCl_4$ (1.88 ml, 1 M) in methylene chloride (9 ml) at 0° C, was added $Ti(OiPr)_4$ (0.9 ml) dropwise over 15 min, followed by diisopropylethylamine (0.44 ml). After an additional 20 min, the compound of Ex. 328, Part C (0.95g, 2.38 mmol) was added in one portion and the resulting mixture was allowed to stir for 1h at 0° C. Tert-butyl acrylate (0.52 ml, 3.57 mmol) was added, and the cooling bath was removed, followed by stirring at room temperature for 12 h. The reaction was quenched with saturated aqueous ammonium chloride solution; the aqueous layer was separated and extracted with methylene chloride. The combined organics were then washed again with saturated ammonium chloride solution, water and brine. The solution was dried over anhydrous magnesium sulfate, filtered and evaporated to give a crude oil which was purified by MPLC (25% ethyl acetate/hexane) to provde tghe Michael addition product as an oil (0.886 g). IR (KBr) 3060, 3028, 1780, 1726, 1694 cm^{-1}; $[\alpha]_D$ = +62.3 (c. 0.32, methanol); HRMS calculated 528.274999, found 528.274957.

E. 4(S)-t-butoxycarbonyl-2(R)-[2-[(1,1'-biphenyl)yl]-ethyl]butanoic acid

To a solution of the compound of Ex. 328, Part D (5.71 g, 10.8 mmol) in THF(67 ml) and water(17 ml) cooled to 0° C was added a mixture of 30% H_2O_2 (8.8 ml) and lithium hydroxide (43.3 mmol). The solution was evaporated after

1.5 h, and the resulting material acidified with 10% citric acid. The organic material was extracted with ethyl acetate, washed with water and brine and dried over anhydrous magnesium sulfate. Filtration and removal of solvent gave a slurry containing 4(S)-phenylmethyloxazolidin-2-one and crude product. Addition of ether and a seed crystal of 4(S)-(phenylmethyl)oxazolidinone followed by cooling to -20, gave a solid precipitate which was removed by filtration. The product was further purified by conversion to its dicyclohexylamine salt and recrystallization from ether. The salt was then treated with 5% $KHSO_4$ to give the acid as a crystalline product that could be used without further purification in the next step.

F. 4(S)-t-butoxycarbonyl-4-butyl-2(R)-[2-[(1,1'-biphenyl)yl]ethyl]butanoic acid

To a stirred, cooled (-78° C) solution of the compund of Ex. 328, Part E (1.01 g, 2.73 mmol) in THF(20 ml)/DMPU(5 ml), was added LDA (5.46 ml, 1 M soln) over 10 min. Following the addition, the solution was allowed to stir for 1 h at -40° C. Butyl iodide (0.31 ml, 2.73 mmol) was added, and the solution allowed to gradually reach room temp over 12 h. The crude material was then poured into 10% citric acid and extracted with ethyl acetate. The combined organics were washed with water, brine and then dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave the desired product as 4:1 mixture of diastereomers which could be separated directly by HPLC on silica gel or alternately, by conversion to the benzyl ester and MPLC purification as described in WO94/12169. $[\alpha]_D$ = + 20 (c. 0.20, methanol); IR (kBr) 3028, 1726, 1602; HRMS calculated 425.269185, found 425.269228.

G. 2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4(S)-t-butoxycarbonyl-4-butyl-1-oxobutyl]-hexahydropyridazine

To a stirred, cooled (-20° C; CCl_4/CO_2) solution of the compound of Ex. 328, Part F, (0.297 grams) and pyridine (56mL) in anhydrous methylene chloride (5 mL) was added cyanuric fluoride (0.19 g) over one minute. The reaction was stirred 1.5 hours at -20°, filtered and washed with ice water. The aqueous was extracted 2X with methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure affording a clear oil (0.301 g). ^1H NMR in $CDCl_3$ was consistent with a clean conversion to the acid fluoride which was carried on without further characterization or purification. The acid fluoride thus obtained was dissolved in anhydrous methylene chloride (1 mL) and added to a previously mixed solution of piperazic acid (0.185 g) and diisopropylethylamine (0.24 mL) in anhydrous methylene chloride (5 mL). The reaction was allowed to stir at room temperature overnight. The reaction was poured into 10% aqueous citric acid and extracted three times with methylene chloride. The combined organic phases were washed with water and saturated brine, dried over anhydrous magnesium sulfate, filtered, and solvent was removed under reduced pressure. The resulting material was purified via preparative layer chromatography (EM plates, 1mm silica gel with 0.25mm concentration zone) eluting 2X with 2% MeOH in $CHCl_3$ to afford the desired product as an oil (0.060 mg). HRMS calculated 671.369628, found 671.368562, IR (KBr) 3062, 3030, 1724, 1674 cm^{-1}.

H. 2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4(S)-t-butoxycarbonyl-4-butyl-1-oxobutyl]-3-(methylaminocarbonyl)hexahydropyridazine

To a stirred, cooled (-20 °C) solution of the compound of Ex. 328, Part G (0.059 g) in anhydrous THF

(2 mL) was added N-methylmorpholine (10 mL) followed in 15 minutes by isobutylchloroformate (12 mL). The reaction was stirred 35 minutes at -20° C at which time a 40 % aqueous solution of monomethylamine (31 mL) was added. The reaction was stirred 45 minutes at room temperature and then the volatile components were removed under reduced pressure. The residue was taken up in ethyl acetate, washed with 10% aqueous citric acid, water, saturated brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure affording the N-methyl amide (0.050 g). HRMS calculated 684.401262, found 684.399793.

I. 2-[2(R)-[2-[(1,1'-biphenyl)yl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonylhexahydropyridazine

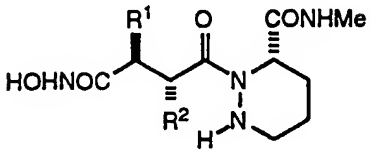
Trifluoroacetic acid (2 mL) was added to the amide of Ex. 328, Part H (0.050 g), and the reaction was stirred for 1 hour at room temperature at which time the volatiles were removed under reduced pressure affording free acid (0.040 g) which was used without further purification.

To a stirred solution of the crude acid (0.039 g) in methanol (2 mL) was added 10 % palladium on carbon (10-15 mg). The mixture was stirred for one hour undera atm hydrogen (at which time it was filtered and the volatiles were removed under reduced pressure. The residue was chromatographed on 1mm EM preprative chromatography plates with a 0.25 mm concentration zone eluting 2 times in 7.5 % MeOH in $CHCl_3$ to provide the title compound (0.019 grams). HRMS calculated 494.301882, found 494.300034.

Using the above-described techniques or variations thereon appreciated by those of skill in the art of

chemical synthesis, the compounds of Tables 1-3 (shown below) can also be prepared.

Table 1

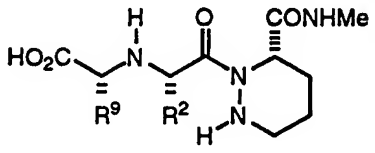


Ex. No.	R^1	R^2
1E	methyl	isobutyl
4	benzyl	isobutyl
5	phenyoxymethyl	isobutyl
6	phenylthiomethyl	isobutyl
7	benzylthiomethyl	isobutyl
8	2-thienylthiomethyl	isobutyl
9	acetoxymethyl	isobutyl
10	isobutyryloxymethyl	isobutyl
11	t-butyryloxymethyl	isobutyl
12	thioacetoxymethyl	isobutyl
13	thioisobutyryl-methyl	isobutyl
14	thio-t-butyryl-methyl	isobutyl
15	2-pyridylmethyl	isobutyl
16	3-pyridylmethyl	isobutyl
17	4-pyridylmethyl	isobutyl
18	benzyl	hexyl
19	phenyoxymethyl	hexyl
20	phenylthiomethyl	hexyl
21	benzylthiomethyl	hexyl
22	2-thienylthiomethyl	hexyl
23	acetoxymethyl	hexyl
24	isobutyryloxymethyl	hexyl
25	t-butyryloxymethyl	hexyl
26	thioacetoxymethyl	hexyl
27	thioisobutyryl-methyl	hexyl
Ex. No.	R^1	R^2

28	thio-t-butyryl-methyl	hexyl
29	2-pyridylmethyl	hexyl
30	3-pyridylmethyl	hexyl
31	4-pyridylmethyl	hexyl
32	benzyl	phenethyl
33	phenyoxymethyl	phenethyl
34	phenylthiomethyl	phenethyl
35	benzylthiomethyl	phenethyl
36	2-thienylthiomethyl	phenethyl
37	acetoxymethyl	phenethyl
38	isobutyryloxymethyl	phenethyl
39	t-butyryloxymethyl	phenethyl
40	thioacetoxymethyl	phenethyl
41	thioisobutyryl-methyl	phenethyl
42	thio-t-butyryl-methyl	phenethyl
43	2-pyridylmethyl	phenethyl
44	3-pyridylmethyl	phenethyl
45	4-pyridylmethyl	phenethyl
45a	H	phenylpropyl
46	benzyl	phenylpropyl
47	phenyoxymethyl	phenylpropyl
48	phenylthiomethyl	phenylpropyl
49	benzylthiomethyl	phenylpropyl
50	2-thienylthiomethyl	phenylpropyl
51	acetoxymethyl	phenylpropyl
52	isobutyryloxymethyl	phenylpropyl
53	t-butyryloxymethyl	phenylpropyl
54	thioacetoxymethyl	phenylpropyl
55	thioisobutyryl-methyl	phenylpropyl
56	thio-t-butyryl-methyl	phenylpropyl
57	2-pyridylmethyl	phenylpropyl
Ex. No.	R^1	R^2

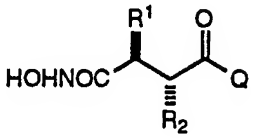
58	3-pyridylmethyl	phenylpropyl
59	4-pyridylmethyl	phenylpropyl
60	methyl	octyl
61	phenylthiomethyl	octyl
62	benzylthiomethyl	octyl
63	2-thienylthiomethyl	octyl
64	acetoxymethyl	octyl
65	isobutyryloxymethyl	octyl
66	t-butyryloxymethyl	octyl
67	thioacetoxymethyl	octyl
68	thioisobutyryl-methyl	octyl
69	thio-t-butyryl-methyl	octyl
70	2-pyridylmethyl	octyl
71	3-pyridylmethyl	octyl
72	4-pyridylmethyl	octyl
73	H	isobutyl
74	methyl	phenethyl

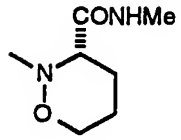
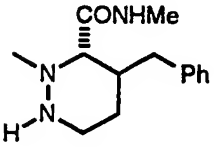
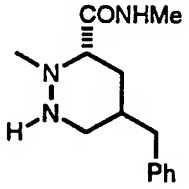
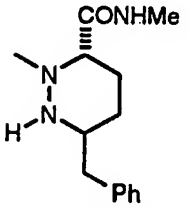
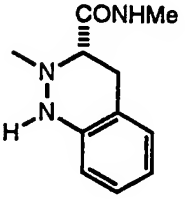
Table 2

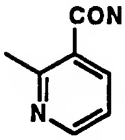
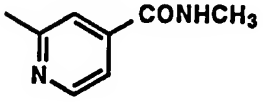
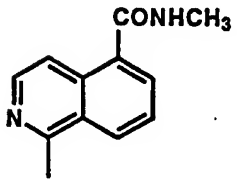
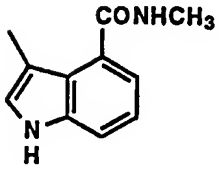


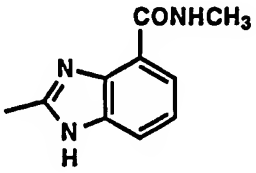
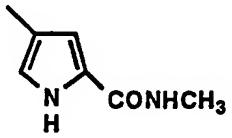
Ex. No.	R^2	R^9
201	isobutyl	methyl
202	n-hexyl	methyl
203	n-heptyl	methyl
204	n-octyl	methyl
205	phenethyl	methyl
206	phenylpropyl	methyl
207	isobutyl	benzylthiomethyl
208	n-hexyl	benzylthiomethyl
209	phenethyl	benzylthiomethyl
210	phenylpropyl	benzylthiomethyl
211	isobutyl	benzyloxymethyl
212	n-hexyl	benzyloxymethyl
213	phenethyl	benzyloxymethyl
214	phenylpropyl	benzyloxymethyl
215	phenethyl	benzyl
216	phenethyl	isobutyl
217	isobutyl	methyl
218	phenethyl	3-[(4-methylphenyl)-sulfonyl]propyl
219	2-[(4-phenyl)phenoxy]-ethyl	methyl

Table 3



Ex. No.	R^1	R^2	Q
301	methyl	isobutyl	
302	methyl	isobutyl	
303	methyl	isobutyl	
304	methyl	isobutyl	
305	methyl	isobutyl	
306	H	isobutyl	phenyl
307	H	isobutyl	2-pyridyl

Ex. No.	R^1	R^2	Q
308	H	isobutyl	
309	H	isobutyl	
310	H	isobutyl	1-isoquinolinyl
311	H	isobutyl	2-quinolinyl
312	H	isobutyl	
313	H	isobutyl	3-indolyl
314	H	isobutyl	

Ex. No.	R^1	R^2	Q
315	H	isobutyl	2-benzimidazolyl
316	H	isobutyl	
317	H	isobutyl	2-pyrrolyl
318	H	isobutyl	2-imidazolyl
319	H	isobutyl	
320	H	isobutyl	5-indolyl
321	H	isobutyl	5-imidazolyl

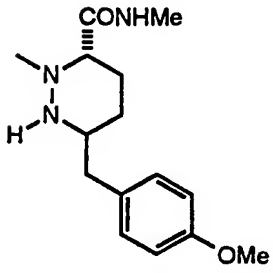
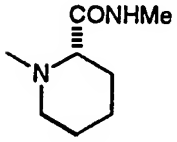
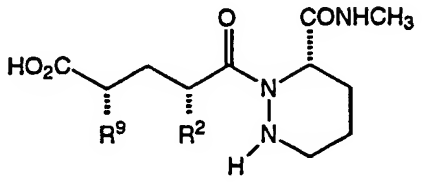
Ex. No.	R^1	R^2	Q
322	methyl	isobutyl	
323	OH	isobutyl	

Table 4



Ex. No.	R^9	R^2
401	Me	2-(1,1'-biphenyl)ylethyl
402	n-Bu	2-(1,1'-biphenyl)ylethyl
403	n-Bu	2-(1,1'-biphenyl)ylpropyl
404	n-Bu	2-[(4-propyl)phenyl]ethyl
405	n-Bu	2-[(4-butyl)phenyl]ethyl
406	n-Bu	2-[(4-t-butyl)phenyl]ethyl
407	n-Bu	2-[(4-fluorophenyl)phenyl]ethyl
408	Me	2-[(4-fluorophenyl)phenyl]ethyl
409	Me	n-octyl
410	n-Bu	2-[(4-thiazolyl)phenyl]ethyl
411	Me	2-[(4-thiazolyl)phenyl]ethyl
412	$PhSO_2(CH_2)_3$-	2-[(4-thiazolyl)phenyl]ethyl
413	$Ph(CH_2)_3$-	2-[(4-thiazolyl)phenyl]ethyl
414	n-Bu	2-[(4-oxazolyl)phenyl]ethyl
415	Me	2-[(4-oxazolyl)phenyl]ethyl
416	$PhSO_2(CH_2)_3$-	2-[(4-oxazolyl)phenyl]ethyl
417	$Ph(CH_2)_3$-	2-[(4-oxazolyl)phenyl]ethyl
418	n-Bu	2-[(4-imidazolyl)phenyl]ethyl
419	Me	2-[(4-imidazolyl)phenyl]ethyl
420	$PhSO_2(CH_2)_3$-	2-[(4-imidazolyl)phenyl]ethyl
421	$Ph(CH_2)_3$-	2-[(4-imidazolyl)phenyl]ethyl
422	n-Bu	2-[4-(dimethylamino)methyl-phenyl]ethyl
423	Me	2-[4-(dimethylamino)methyl-phenyl]ethyl
424	$PhSO_2(CH_2)_3$-	2-[4-(dimethylamino)methyl-phenyl]ethyl
425	$Ph(CH_2)_3$-	2-[4-(dimethylamino)methyl-phenyl]ethyl

UTILITY

The compounds of formula I possess matrix metalloproteinase and/or TNF inhibitory activity. The MMP-3 inhibitory activity of the compounds of the present invention is demonstrated using assays of MMP-3 activity, for example, using the assay described below for assaying inhibitors of MMP-3 activity. The compounds of the present invention are bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of formula I have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention are also useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MMP-3. These would be provided in commercial kits comprising a compound of this invention.

Matrixmetalloproteinases have also been implicated in the degradation of basement membrances to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis. (Stetler-Stevenson, Cancer and Metastasis Reviews, 9, 289-303, 1990.) The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention would also have utility for the prevention and treatment of osteopenia associated with matrixmetalloproteinase-mediated breakdown of cartilage and bone which occurs in osteoporosis patients.

Compounds which inhibit the production or action of TNF and/or MMP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases. These

include, but are not limited to inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, an acute infection, septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, crohn's disease, mycobacterial infection, meningitis, psoriasis, periodontits, gingivitis, congestive heart failure, fibrotic disease, cachexia, and aneroxia, graft rejection, cancer, corneal ulceration or tumor invasion by secondary metastases, autoimmune disease, osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, and hyperoxic alveolar injury.

The compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF Induction in Mice described below.

As used herein "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC_{50} or K_i value of less than about 1 mM for the inhibition of MMP-3.

Bisacetylated Substance P / MMP-3 fluorescent assay

A high capacity enzymatic assay was developed to detect potential inhibitors of MMP-3. The assay uses a derivative of a peptide substrate, substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met), which is cleaved by MMP-3 exclusively at the glutamine-phenylalanine bond. In order to adapt this assay for high throughput screening, we have developed a fluorimetric method of product detection. The production of the hydrolysis product, substance P 7-11, is measured by reaction with

fluorescamine, a fluorogenic compound which reacts with the primary amine of this fragment. The substance P substrate is bisacetylated to block the primary amines of the intact substrate. Thus, the resulting fluorescence represents generation of product (7-11 peptide) formed upon cleavage by MMP-3, and is quantitated using a standard curve prepared with known concentrations of 7-11 peptide. Kinetic studies using the bisacetylated substrate yield the following parameters for MMP-3: Km =769 +/- 52 uM; Vmax = 0.090 +/- 0.003 nmoles 7-11 peptide/min.

To evaluate inhibition of MMP-3, compounds were prepared at a concentration of 10 mM in 100% methanol, and then further diluted to a 20X molar stock. Five microliters of each drug stock was added to the assay in the presence of 20 nM truncated MMP-3 in 67.5 mM tricine (pH 7.5), 10 mM $CaCl_2$, 40 mM NaCl, and 0.005% Brij 35 in a final volume of 100 microliters. Bisacetylated substance P (1000 mM) was added, and the assay was run for 1 hour at 25°C. The reaction was quenched with EDTA (20 mM) and product was detected fluorometrically following addition of fluorescamine (0.075 mg/ml). Fluorescence of each sample was converted to an amount of product formed using a substance P 7-11 standard curve. Under these conditions, the assay is linear with respect to MMP-3 amount up to 10 pmoles. Inhibition of MMP-3 was determined by comparing the amount of product generated in the presence and absence of compound.

Activities of representative compounds of the invention in the above assay are shown in Table A below. The K_i values are indicated as follows: +++ = <50 nM; ++ = 50 nM to 100 nM; + = >100nM.

Table A

Ex. No.	K_i
73	++
1E	++

2	+++
45a	+
4	+++
205	+
215	+
216	+
217	+
218	++
219	++
402	++

Ex vivo assay for bioavailability of MMP-3 inhibitors

Blood was collected by cardiac puncture from rats at different times after dosing I.V., I.P., or P.O. with compound in order to determine the levels of inhibitor present. Plasma was extracted with 10% TCA in 95% methanol, and placed on ice for 10 minutes. The plasma was then centrifuged for 15 minutes at 14,000 rpm in an Eppendorf microcentrifuge. The supernatant was removed, recentrifuged, and the resulting supernatant was diluted 1:10 in 50 mM tricine, pH 8.5. The pH of the sample was adjusted to 7.5, and then assayed in the MMP-3 substance P fluorescent enzymatic assay. Plasma from naive rats was extracted by the same method and used as a negative control. This plasma was also used to prepare a spiked plasma curve of the compound of interest. Known concentrations of the compound were added to control plasma, the plasma was extracted by the same method, and then assayed in the MMP-3 enzymatic assay. A standard curve was prepared that related percent inhbition in the MMP-3 assay to the concentration of drug added in the spiked samples. Based on the percent inhibition in the presence of plasma from dosed rats, the concentration of compound was determined using the standard curve.

Table B shows the results of dosing of representative compounds of the invention orally in rats at 100 mg/kg.

Table B

Ex. No.	C_{max} (μg/ml)
73	3.2
1E	1.8
4	1.7

Acute Cartilage Degradation Rat Model

An in vivo model of acute cartilage degradation in rats has been characterized as a method to determine the proteoglycan content in the synovial fluid after the induction of cartilage degradation. Experimental groups exhibit increased levels of proteoglycan content in their synovial fluid versus control rats. The criteria to demonstrate a compound's activity in this model, is the ability to inhibit the demonstration of cartilage degradation, as measured by increased proteoglycan content in the synovial fluid of rats after compound administration. Indomethacin, a non-steroidal anti-inflammatory drug is inactive in this model. Indomethacin administration does not inhibit the demonstration of cartilage degradation in experimental animals. In contrast, administration of a compound of this invention significantly inhibited the demonstration of cartilage degradation in this model.

TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 μg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the

present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, MMP-3, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a

pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches wall known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery

system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems,

such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be

manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150

milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

	Wt. %
Active Ingredient	10
Liquid Sugar	50
Sorbitol	20
Glycerine	5
Flavor, Colorant and Preservative	as required
Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.01
Keltrol® (Food Grade Xanthan Gum)	0.2
Liquid Sugar	5
Flavor, Colorant and Preservative	as required
Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

	Wt. %
Active Ingredient	50.0
Lactose	35.0
Sugar	10.0

Acacia	4.7
Sodium Carboxylmethylcellulose	0.3

Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.02
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

	Wt. %
Active Ingredient	10
Gelcarin® (Carrageenin gum)	1
Sodium Saccharin	0.01
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

	Wt. %
Active Ingredient	30
Tween® 80 and Span® 80	6
Keltrol®	0.5
Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5%

by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second

therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above. Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released

component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that

unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

The term "consisting essentially of" where used in the present disclosure is intended to have its customary meaning; namely, that all specified materials and conditions are very important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

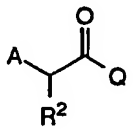
The foregoing disclosure includes all the information deemed essential to enable those of skill in the art to practice the claimed invention. Because the cited references may provide further useful information, however, these cited materials are hereby incorporated by reference.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

CLAIMS

What is claimed:

1. A method of treating osteoarthritis or rheumatoid arthritis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I:



Formula I

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

A is selected from $-N(R^8)CH(R^9)CO_2H$ or $-CH(R^{11})C(R^{9a})(R^9)CO_2H$, $-C(R^1)(R^{1a})CONHOH$;

Q is selected from:

a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or

a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^1 is selected from:

H, halogen

C_1-C_{10} alkyl substituted with 0-3 R^4,

C_2-C_{10} alkenyl substituted with 0-3 R^4,

C_2-C_{10} alkynyl substituted with 0-3 R^4,

C_6-C_{10} aryl,
C_3-C_6 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, piperidinyl, pyrimidinyl or pyridazinyl, pyrrolidinyl, triazolidinyl, oxadiazolidinyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{1a} is selected from H, R^1, $NR^{10}R^{10a}$, OR^{17} or $S(O)_mR^{17}$

Alternately R^1 and R^{1a} can be taken together to form a 3-7 membered carbocyclic or a 5-7 membered, saturated heterocyclic ring, said heterocyclic ring containing 1-2 heteroatoms selected from N, O, and S, and optionally substituted at carbon with keto;

R^2 is selected from:
C_2-C_{10} alkyl substituted with 0-3 R^{17b},
$(-CH_2)_nO-(C_1-C_8$ alkyl$)-R^{20}$, or
$(-CH_2)_nS-(C_1-C_8$ alkyl$)-R^{20}$,
$-(CH_2)_nOR^{20}$,
$-(CH_2)_nSR^{20}$,
$-(CH_2)_nS-(C_1-C_6)$ alkyl, or
$-(CH_2)_nO-(C_1-C_6)$ alkyl;

n=0-8

R^3 is selected from: OR^{11}, $NHCH(R^{12})COR^{13}$, $NHCH(R^{12})COOR^{11}$, $NHCH(R^{12})CONR^{14}R^{15}$, $NR^{10}R^{10a}$;

R^4 is selected from:
$-OR^{17a}$, $-SO_mR^{17a}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},

C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{18};

m=0-2;

R^{4a} is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_1-C_4 alkylcarbonyl,
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^5 and R^6 are independently selected from:
hydrogen,
hydroxy,
C_1-C_6 alkyl substituted with 0-3 R^{20},
phenyl,

C_7-C_{14} arylalkyl,
C_7-C_{14} arylalkoxy,
C_1-C_4 alkylcarbonyl,
C_7-C_{14} arylalkoxycarbonyl,
C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$,
C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$,
C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$,
=O, =S, or a ketal or thioketal form thereof when R^5 or R^6 are attached to a saturated carbon atom, or = O when R^5 or R^6 is attached to sulfur;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein said heterocyclic ring contains one or two N, O or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
alkylaminocarbonyl,
arylsulfonyl,
heteroarylalkoxycarbonyl,
cycloalkoxycarbonyl,
heteroarylsulfonyl,
alkyesulfonyl,
cycloalkylsulfonyl,

R^9 is selected from:
H,
C_1-C_8 alkyl substituted with 0-3 R^{4a},
C_2-C_8 alkenyl substituted with 0-3 R^{4a},
C_2-C_8 alkynyl substituted with 0-3 R^{4a};

R^{9a} is selected from H, OR^{17}, SR^{17} or NR^{10} R^{10a},

Alternately R^9 and R^{9a} can be taken together to form a 3-7 membered carbocyclic or heterocyclic ring, said heterocyclic ring containing 1-2 heteroatoms selected from N, O or S, optionally substituted on carbon with keto;

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4 or
C_1-C_6 alkylcarbonyl;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,
C_1-C_4 alkyl substituted with 0-3 R^4,
C_2-C_4 alkenyl substituted with 0-3 R^4,
C_2-C_4 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,

C_1-C_6 alkyl substituted with 0-3 R^{17A}
C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
H,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

phenyl, optionally substituted with halogen, C_1-C_4 alkyl, C_1-cyalkoxy, hydroxy, or $-NR^{10}R^{10a}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$, =O or =S when attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl,

$-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$;

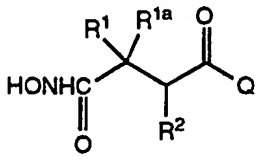
R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl,

$-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl; and

R^{20} is selected from:
aryl substituted with 0-5 R^{18},
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

2. A compound of Formula II:



Formula II

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

Q is selected from:
a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or
a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said

heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^1 is selected from:

H, halogen

C_1-C_{10} alkyl substituted with 0-3 R^4,

C_2-C_{10} alkenyl substituted with 0-3 R^4,

C_2-C_{10} alkynyl substituted with 0-3 R^4,

C_6-C_{10} aryl,

C_3-C_6 cycloalkyl, or

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{1a} is selected from H, $NR^{10}R^{10a}$, OR^{17} or $S(O)_mR^{17}$

Alternately R^1 and R^{1a} can be taken together to form a 3-7 membered carbocyclic or heterocyclic ring, said heterocyclic ring containing 1-2 hetero-atoms selected from N, O, and S;

R^2 is selected from:

C_2-C_{10} alkyl substituted with 0-3 R^{17b},

$(-CH_2)_nO-(C_1-C_8$ alkyl$)-R^{20}$, or

$(-CH_2)_nS-(C_1-C_8$ alkyl$)-R^{20}$,

$-(CH_2)_nOR^{20}$,

$-(CH_2)_nSR^{20}$,

$-(CH_2)_nS-(C_1-C_6)$ alkyl, or

$-(CH_2)_nO-(C_1-C_6)$ alkyl;

n=0-6

R^3 is $-NR^{10}R^{10a}$

R^4 is selected from:
OR^{17}, SO_mR^{17}, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

m=0-2;

R^5 and R^6 are independently selected from:
hydrogen, hydroxy, C_1-C_6 alkyl substituted with 0-3 R^{20}, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, C_7-C_{14} arylalkoxycarbonyl, C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$, C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$, C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered

carbocyclic or heterocyclic ring, wherein the heterocyclic ring contains one to two N, O, or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
arylsulfonyl,
heteroarylsulfonyl,
cycloakoxycarbonyl,
keteroarylalkoxycarbonyl,
alkylsulfonyl, or
cycloalkylsulfonyl;

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from:
H,
C_1-C_4 alkyl substituted with 0-3 R^4,
C_2-C_4 alkenyl substituted with 0-3 R^4,
C_2-C_4 alkynyl substituted with 0-3 R^4;

R^{13} is C_1-C_4 alkyl;

R^{14} and R^{15} are independently selected from H or C_1-C_4 alkyl;

R^{16} is hydrogen or methyl;

R^{17} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{17A}
C_1-C_6 alkylcarbonyl substituted with 0-3 R^{17A},
C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{17A},
phenoxycarbonyl substituted with 0-3 R^{18};

R^{17a} is selected from:
H,
C_1-C_4 alkyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, isothiazolyl, thiazolinyl,
thiazolidinyl, isothiazolinyl, piperidinyl,
pyrimidinyl, pyridazinyl, pyrazinyl,
pyrrolidinyl, pyrrolyl, N-methylpyrrolyl,
triazolyl, triazolidinyl, oxazolyl,
isoxazolyl, oxazolinyl, isoxazolinyl,
oxazolidinyl, oxadiazolyl, oxadiazolidinyl,
imidazolyl, imidazolidinyl, said heterocyclic
ring system being substituted with 0-5 R^{19};

R^{17b} is selected from:
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl
a heterocycle selected from the group consisting of
thienyl, pyridinyl, morpholinyl, furyl,
thiazolyl, isothiazolyl, thiazolinyl,
thiazolidinyl, isothiazolinyl, piperidinyl,

pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^{18}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

phenyl, optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or $NR^{10}R^{10a}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{18} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted on the aliphatic carbons with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$ =0 or =S when

attached to a saturated carbon atom, or =O when attached to sulfur;

R^{18}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

R^{19}, when a substituent on carbon, is selected from one or more of the following:

phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, sulfonamide, C_1-C_4 alkyl substituted with $-NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_1-C_4 hydroxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-S(O)_mR^{11}$, $-NHSO_2R^{11}$,

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

or R^{19} may be a 3- or 4- carbon chain attached to adjacent carbons on the ring to form a fused 5- or 6-membered ring, said 5- or 6- membered ring being optionally substituted with

halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, $-NR^{10}R^{10a}$;

R^{19}, when a substituent on nitrogen, is selected from one or more of the following:

phenyl, benzyl, phenethyl, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, $-CH_2NR^{10}R^{10a}$, $-NR^{10}R^{10a}$, C_2-C_6 alkoxyalkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, $-CO_2H$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl;

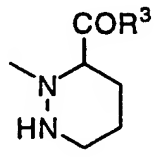
R^{20} is selected from:

aryl substituted with 0-5 R^{18},

a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

with the following proviso:

when R^1 and R^{1a} are both hydrogen and Q is



then R^2 is not hydrogen, C_3-C_{10} alkyl or (C_1-C_4 alkyl)aryl.

3. A compound of Claim 2 wherein:

Q is a 5-7 membered saturated heterocyclic ring system containing at least one nitrogen and optionally containing an additional heteroatom selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^1 is selected from:
H,
C_1-C_4 alkyl substituted with 0-3 R^4;

R^2 is selected from:
C_2-C_4 alkyl substituted with 0-3 R^{17b},
$-O-(C_1-C_6$ alkyl$)-R^{20}$,
$-S-(C_1-C_6$ alkyl$)-R^{20}$,
$-CH_2O-(C_1-C_5$ alkyl$)-R^{20}$, or
$-CH_2S-(C_1-C_5$ alkyl$)-R^{20}$;

R^8 is hydrogen;

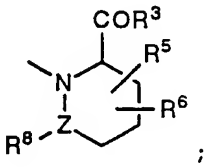
R^{10} is selected from:
hydrogen,
C_1-C_6 alkyl substituted with 0-4 R^4;

4. A compound of Claim 3 wherein:

Q is a heterocycle selected from hexahydro-1-pyridazinyl, 2-tetrahydro-1,2-oxazinyl, 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methylpiperazinyl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl-1-oxide, tetrahydro-1,4-thiazin-4-yl-1,1-dioxide, 1-oxa-2-piperidinyl, said heterocycle being substituted with 0-3 groups selected from $-C(=O)R^3$, R^5, R^6, or R^8.

5. A compound of claim 4 wherein:

Q is



;

Z is N or O;

R^5 is selected from:
hydrogen, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, or C_7-C_{14} arylalkoxycarbonyl; and

R^6 is hydrogen;

with the proviso that R^8 is absent when Z is O.

6. A compound of Claim 2 selected from the group consisting of:

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,
[4-(N-hydroxyamino)-2R-isobutyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-hexyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-ethylphenyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-(methylthio-2-thienyl)succinyl]-N^1-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl acetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl isopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thioacetate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thioisopropanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-octyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid-N-methyl amide,

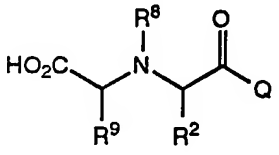
[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-4'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-5'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-6'(S/R)-benzylpiperazic acid-N-methyl amide,

[4-(N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-[5',6']benzopiperazic acid-N-methyl amide,

7. A compound of formula III:



Formula III

or pharmaceutically acceptable salts or prodrug forms thereof, wherein:

Q is selected from:
a C_5-C_{14} carbocyclic ring system substituted with 0-4 groups selected from R^5, R^6, R^{18} or $-C(=O)R^3$, or
a 5- to 10-membered heterocyclic ring system containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen or sulfur, said heterocyclic ring system being substituted with 0-4 groups selected from R^5, R^6, R^8, R^{19} or $-C(=O)R^3$;

R^2 is selected from
C_1-C_8 alkyl substituted with 0-3 R^{17b},
C_1-C_8 alkenyl substituted with 0-3 R^{17b},
C_1-C_8 alkynyl substituted with 0-3 R^{17b},
$-(CH2)_n-O-(C_1-C_8$ alkyl),
$-(CH2)_n-S-(C_1-C_8$ alkyl),
$-(CH_2)_nO-(C_1-C_8$ alkylene)$-R^{20}$,
$(CH_2)_nS(C1-C8$ alkylene)$-R^{20}$
$-(CH_2)_nOR^{20}$, or
$-CH_2)_nSR^{20}$

n=1-8

R^3 is $NR^{10}R^{10a}$;

R^4 is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
$-NR^8R^{10}$, $-NHC(=NR^8)N(R^8)R^{10}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, piperidinyl, pyrimidinyl or

pyridazinyl, said heterocyclic ring system being substituted with 0-2 R^{19};

m= 0-2;

R^{4a} is selected from:
$-OR^{17}$, $-SO_mR^{17}$, $-CO_2R^{12}$, $-CONR^{10}R^{10a}$,
C_1-C_4 alkyl,
C_1-C_4 alkylcarbonyl,
aryl substituted with 0-5 R^{18},
C_3-C_8 cycloalkyl, or
a heterocycle selected from the group consisting of thienyl, pyridinyl, morpholinyl, furyl, thiazolyl, isothiazolyl, thiazolinyl, thiazolidinyl, isothiazolinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolidinyl, pyrrolyl, N-methylpyrrolyl, triazolyl, triazolidinyl, oxazolyl, isoxazolyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxadiazolyl, oxadiazolidinyl, imidazolyl, imidazolidinyl, said heterocyclic ring system being substituted with 0-5 R^{19};

R^5 and R^6 are independently selected from:
hydrogen, hydroxy, C_1-C_6 alkyl substituted with 0-3 R^{20}, phenyl, C_7-C_{14} arylalkyl, C_7-C_{14} arylalkoxy, C_1-C_4 alkylcarbonyl, C_7-C_{14} arylalkoxycarbonyl, C_1-C_4 alkoxy, $-NR^{14}R^{15}$, $-COOR^{11}$, C_1-C_4 alkoxycarbonyl, hydroxymethyl, $-CH_2OR^{13}$, C_1-C_4 alkylaminocarbonyl, $-C(=NOH)R^{14}$, =O, =S, or a ketal or thioketal form thereof when R^5 or R^6 are attached to a saturated carbon atom, or = O when R^5 or R^6 is attached to sulfur;

R^5 and R^6 when attached to adjacent atoms on the ring can alternately join to form a 5-7 membered carbocyclic or heterocyclic ring, wherein the

heterocyclic ring contains one or two N, O or S atoms, said carbocyclic or heterocyclic ring being substituted with 0-2 R^{18};

R^8 is a substituent on nitrogen and is selected from hydrogen,
C_1-C_6 alkyl substituted with 0-3 R^{20},
C_1-C_6-alkylcarbonyl,
alkoxycarbonyl,
arylalkoxycarbonyl,
alkylaminocarbonyl,
arylsulfonyl,
heteroarylsulfonyl,
cycloakoxycarbonyl,
keteroarylalkoxycarbonyl,
alkylsulfonyl, or
cycloalkylsulfonyl;

R^9 is selected from:
H,
C_1-C_5 alkyl substituted with 0-3 R^{4a},
C_2-C_5 alkenyl substituted with 0-3 R^{4a},
C_2-C_5 alkynyl substituted with 0-3 R^{4a};

R^{10} is selected from:
hydrogen,
C_1-C_4 alkoxy,
C_1-C_6 alkyl substituted with 0-4 R^4;

R^{10a} is selected from hydrogen or C_1-C_4 alkyl;

R^{10} and R^{10a} can alternatively join to form $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH_2N(R^{16})CH_2CH_2-$, or $-CH_2CH_2OCH_2CH_2-$;

R^{11}, is H, benzyl, or C_1-C_4 alkyl;

R^{12} is selected from: